Overarching Issues that Render the Conclusions Reached in the Draft IRIS Toxicological Review of Formaldehyde – Review (EPA/635/R-21/286a) Flawed and Unreliable Without Significant Revision

1. **THE DRAFT ASSESSMENT DID NOT INCORPORATE RECOMMENDATIONS, COMMENTS, AND GUIDANCE PROVIDED BY THE NATIONAL ACADEMIES ON THE 2010 DRAFT OF THE IRIS FORMALDEHYDE ASSESSMENT.**
2. **AN INCOMPLETE SYSTEMATIC REVIEW CALLS INTO QUESTION THE FOUNDATION OF CONCLUSIONS REACHED IN THE DRAFT ASSESSMENT**
3. **THE DRAFT ASSESSMENT INHIBITS THE REVIEWERS ABILITY TO SEPARATE SUBJECTIVITY FROM OBJECTIVITY IN THE CONCLUSIONS REACHED**
4. **THE EXPERIMENTAL ANIMAL EVIDENCE IS OFTEN INAPPROPRIATELY REJECTED OR DOWN GRADED DUE TO MISINTERPRETATIONS**
5. **The DRAFT ASSESSMENT DID NOT CONSIDER TOXICOKINETICS IN EITHER HAZARD IDENTIFICATION OR DOSE RESPONSE ASSESSMENT. THE DRAFT ASSESSMENT FAILED TO ACKNOWLEDGE THE LACK OF SYSTEMIC DISTRIBUTION OF INHALED FORMALDEHYDE IN AN INTEGRATED MANNER.**
6. **THE DRAFT ASSESSMENT DOES NOT INTEGRATE DOSIMETRY INTO ANALYSIS SUPPORTING HAZARD IDENTIFICATION OR DOSE RESPONSE. IT DOES NOT ACCOUNT FOR ENDOGENOUS PRODUCTION OF FORMALDEHYDE AND THE HOMEOSTATIC STATE IN NORMAL INDIVIDUALS.**
7. **THE DRAFT ASSESSMENT DOES NOT INCORPORATE ALL LINES OF EVIDENCE INTO HAZARD IDENTIFICATION**
8. **THE DRAFT ASSESSMENT DOES NOT INCORPORATE ALL LINES OF EVIDENCE INTO THE DOSE RESPONSE ASSESSMENT AND OBSCURES THE OVERLY CONSERVATIVE EFFECTS OF MODELING**
9. **THE DRAFT ASSESSMENT DOES NOT INTEGRATE INFORMATION ON MOA INTO THE HAZARD IDENTIFICATION OR DOSE RESPONSE AS REQUIRED BY EPA GUIDELINES**

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1. THE DRAFT ASSESSMENT DID NOT INCORPORATE RECOMMENDATIONS, COMMENTS, AND GUIDANCE PROVIDED BY THE NATIONAL ACADEMIES ON THE 2010 DRAFT OF THE IRIS FORMALDEHYDE ASSESSMENT.

Example 1: The Draft Assessment inappropriately combines myeloid and other/unspecified leukemias together into one class which it then refers to as "myeloid leukemia (p. 2-87) contrary to the NAS (2011) recommendation against combining incidence of different leukemia types.

> *Lymphohematopoietic cancers. EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas.*

In direct conflict with previous NAS recommendations, the Draft Assessment (p. 1-423) states:

> *For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia.*

On pages 2-86 and 2-87 the Draft Assessment also inappropriately combines various leukemias, against NAS (2011) recommendations when assessing myeloid leukemia background incidences, as confusingly evidenced by the statement:

> *However, the inclusion of any leukemia subtypes not related to formaldehyde exposure should theoretically dampen the exposure-response relationship (lowering the regression coefficient) relative to that for all the myeloid leukemias alone; thus, this should mitigate at least some of the effect of using the all leukemia background rates.*

Example 2: EPA did not derive, and present for comparison, an RfC for upper respiratory tract effects, based on cytotoxicity, as directed by the NAS (2011):

The NAS (2011) stated:

> *Formaldehyde-induced effects on the respiratory tract demonstrate concentration, time, and site dependence, and these lesions exhibit an anterior to posterior severity gradient (Kerns et al. 1983; Monticello et al. 1996). The committee concludes that the effects for which a candidate RfC should be calculated are histopathologic lesions of the nasal epithelium."*

And

> *None of the human studies demonstrated that exposure duration was important or that a concentration-response relationship was present.*

And

> *The committee recommends that EPA use the animal data to calculate a candidate RfC for respiratory tract lesions in the revised IRIS assessment. That would provide a basis for evaluating the uncertainty associated with the other candidate RfCs that have been calculated.*

And

> *Animal studies in mice, rats, and nonhuman primates clearly show that inhaled formaldehyde at 2 ppm or greater causes cytotoxicity that increases epithelial-cell proliferation and that after prolonged inhalation can lead to nasal tumors. Although the committee agrees with EPA that the human studies that assessed upper respiratory tract pathology were insufficient to derive a candidate RfC, it disagrees with EPA's decision not to use the animal data. The animal studies offer one of the most extensive datasets on an inhaled chemical, and EPA should use the data to derive a candidate RfC for this outcome.*

In conflict with prior NAS comments, in Table 2-10, the Draft Assessment derives two RfCs with uncertainty factors applied for extrapolating subchronic to chronic exposures. NAS clearly and appropriately informed the EPA that an adjustment for exposure duration is not justified.

In addition, the Draft Assessment did not present an RfC for tissue irritation based on cytotoxicity with a No Observed Adverse Effect Level(NOAEL)/Point of Departure (POD) of 1 ppm (and Lowest Observed Adverse Effect Level (LOAEL), as directed by the NAS. Additionally, we find the modeling used for metaplasia observed in the Kerns et al. (1993) study to be opaque. The Draft Assessment chose a NOAEL from observations of compensatory metaplasia (not an adverse reaction event). This had the effect of reducing POD from 1 ppm to a POD of 0.086, an 11.6-fold decrease. This >10x reduction of the NOAEL to a POD moves a NOAEL that is within the range of metabolic saturation to a POD level below metabolic saturation; there is no data-based justification for this change.

Example 3: The revised assessment does not provide clear criteria for evaluating evidence on asthma and provides insufficient support for the classification of formaldehyde as a asthmatogen. The Draft Assessment then calculates several calculate RfCs based on asthma effects (Tale 2-10) without addressing the fundamental issues raised during the NAS (2011) review.

As stated by NAS (2011) regarding the US EPA (2010) draft:

> *Hazard identification is not explicitly based on a guidance document of the agency; the most relevant may be EPA's RfC guidelines (EPA 1994). The ad hoc approach taken in the draft IRIS assessment may reflect inadequate guidance on asthma. Given the limited discussion of the evidence and the lack of clear criteria for evidence evaluation, the committee did not find sufficient support for the hazard identification.*

And,

> *When the studies were conducted, however, the asthma phenotype was not nearly as well characterized as it is now, so although the selected studies were considered by EPA to address asthma, the phenotypic characterizations in children are subject to misclassification when viewed in the context of current understanding.*

In the Draft Assessment Appendices (Table A-51; Evaluation of allergy and Asthma Studies), some studies that were advanced did not provide a clinical evaluation of asthma in the study, but were rated high quality and used to support or develop an RfC for asthma.

> *"Asthma: asthma in past year (wheezing or whistling in the chest or wheezing or whistling chest at night-time or taken asthma treatment in the past year)*

This study clearly was advanced to develop an RfC for asthma and rated with "High Confidence" besides not providing a clinical evaluation of asthma according to any recognized criteria. This continued approach is clearly at odds with the NAS (2011) recommendations.

Example 4: The Draft Assessment did not present an alternative to the RfC based on Krzyzanowski et al. (1990), as directed by the NAS (2011) and does not address the inherently limited reliability of the cross-sectional study design of the study and classified the study confidence as "high."

As stated by NAS (2011):

EPA selected the findings in children (6-15 years old) from the Arizona study by Krzyzanowski et al. (1990) as the basis for the development of a candidate RfC for decreased pulmonary function as measured by PEFR [Peak Expiratory Flow Rate]. The draft IRIS assessment justifies the choice by stating that "the best single study demonstrating decreased pulmonary function is the moderate residential study by Krzyzanowski et al. (1990)" (EPA 2010a, pp. 5-36 to 5-39). The draft discusses only briefly the possibility of using other studies, such as the Kriebel et al. (1993, 2001) studies of anatomy students exposed to formalin. The committee notes that the Krzyzanowski et al. (1990) findings are inherently limited by the cross-sectional nature of their study and found that the study design is not sufficiently described in the published report.

And,

EPA should provide a more thorough analysis and rationale for its choice to advance only the Krzyzanowski et al. (1990) study

Note that the RfC using only data from Krzyanzanowski (1990) is also concerning because it incorporates an uncertainty factor of 3 for intra-human variability. The Draft Assessment includes a benchmark concentration (BMC) analysis with the purpose of addressing intra-human variability, adding another uncertainty adjustment effectively double counts intra-human sensitivity in a sensitive subpopulation.

<u>Example 5: The Draft Assessment Sets Aside the Controlled Human Chamber Studies, in Conflict with NAS (2011) Recommendations.</u>

NAS (2011) also disagreed with exclusion of the chamber studies, when evaluating irritant effects, as stated:

The draft IRIS assessment sets aside the chamber studies as less relevant to derivation of candidate RfCs, but the findings from the studies could be useful, and the committee does not concur with EPA's decision to set them aside.

And

Formaldehyde dehydrogenase is the most important and highly efficient enzyme for detoxification of FA, thereby safeguarding especially against its genotoxicity and carcinogenicity. This essential enzyme is highly conserved in all species. A broad database has demonstrated that in the normal European population no polymorphism exists with impaired FA detoxification. As already discussed in detail in section 7.5.1, FA does not induce or exacerbate asthma in asthmatics at FA concentrations below 1 ppm. Thus, there is no support that asthmatics were at extra risk at relevant concentrations.

The Draft Assessment continues to exclude the chamber data and toxicodynamic data.

Additionally, the NAS identified a lower-bound point of departure for asthma for use in a revised assessment. In contrast, the Draft Assessment presents a POD of 0.06, that is 17 times lower than the lower-bound NOAEL/POD of 1 ppm identified by NAS for assessing potentiation of asthma.

Example 6: The Draft Assessment presents RfCs for a number of non-cancer systemic effects, including reproduction/developmental effects in females and reproductive toxicity in males. NAS (2011) identified this as problematic and not supported by the evidence.

For example, NAS stated:

> *However, the committee is concerned that basing an RfC on a single human study in a minimal human database is problematic. EPA guidelines state that "a reference value based on a single study would likely have a high degree of uncertainty" (EPA 2002, p. 4-20). Although multiple studies of varied quality have assessed spontaneous abortions, the study by Taskinen et al. (1999) is the only one that measured time to pregnancy.*

Despite this recommendation, the Draft Assessment advances and calculates a POD for Taskien et al. (1999), as evidenced in Table 2-1.

Example 7: The Draft Assessment did not follow NAS guidance on evaluating NPC

NAS (2011) addressed the distribution of formaldehyde associated tumors:

> *In Section 4.5.1 of the draft IRIS assessment (EPA 2010a), EPA extends its determination of causality to include all upper respiratory cancers and formaldehyde. EPA does not define what it means by "all upper respiratory cancers," but it might be taken to include cancers of the oral cavity and larynx, as well as nasopharyngeal and sinonasal cancers. That determination was made even though little evidence about any upper respiratory cancer site other than NPC or sinonasal cancer was offered. The committee does not find that determination to be consistent with EPA's cancer guidelines. .... The committee concurs with EPA that there is a lack of sufficient evidence of an increased risk of lung cancer in humans exposed to formaldehyde.*

NAS (2011) also considered the epidemiological Weight of Evidence (WOE) for nasal tumor incidences when stating:

> *The negative findings in the nine other plants (that is, the plants other than the one in Wallingford, Connecticut) need to be considered*

NAS (2011) also provided guidance on the reliability of the Wallingford epidemiology findings (Hauptmann et al., 2004):

> *EPA's carcinogenicity risk-assessment guidelines recommend considering alternative models, especially when biologically based dose-response models are unavailable (EPA 2005). That exercise is especially important when a single study with uncertainties associated with selected cancers and inconsistency with exposure metrics is used.*

Despite this guidance the Draft Assessment concludes that Formaldehyde is a Human Nasal Carcinogen that acts via a genotoxic mechanism, with a linear dose response, and excludes consideration of the cytotoxic and regenerative hyperplasia threshold MOA recently updated by Thompson et al. (2020), as an alternative MOA.

Example 8: The Draft fails to follow NAS (2011) guidance on evaluating leukemia.

NAS (2010) noted:

> *The draft IRIS assessment correctly concludes that formaldehyde is a genotoxic (DNA-reactive) chemical that causes cytogenetic effects, such as mutations. Furthermore, the overall body of evidence suggests that inhaled formaldehyde has a cytogenetic effect that can be detected in peripheral (circulating) blood lymphocytes. However, the committee concludes that data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. First, the observed effects have occurred in highly exposed people, and extrapolating to more typical environmental exposures is difficult given the uncertainty surrounding the form of the dose-response curve for cytogenetic changes. Second, a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established. That gap in mechanistic understanding is particularly problematic because the data strongly suggest that formaldehyde is not available systemically in any reactive form. Thus, the committee can only hypothesize that the observed effects result from an unproven mechanism in portal-of-entry tissues.*

And:

> *The draft IRIS assessment speculates that formaldehyde could reach the bone marrow and cause the mutagenic effects that lead to the cancers noted. However, despite the use of sensitive and selective analytic methods that are capable of differentiating endogenous exposures from exogenous ones, numerous studies have demonstrated that systemic delivery of formaldehyde is unlikely at concentrations that do not overwhelm metabolism. The draft assessment further speculates that circulating hematopoietic stem cells that percolate the nasal capillary bed or nasal associated lymphoid tissues may be the target cells for the mutagenic effects that eventually lead to the cancers noted. However, experimental evidence supporting that mechanism is lacking.*

And

> *Another important topic of discussion in the draft IRIS assessment is that of potential modes of action of formaldehyde as a cause of diverse LHP cancers. As discussed in Chapter 3 of the present report, the available experimental data indicate that formaldehyde itself does not penetrate beyond the superficial layer of the portal of entry, the epithelium of the nasopharynx.*

Since the NAS (2011) review, the EPA (2011) draft IRIS Handbook also addresses the importance of using toxicokinetic information to identify the potential for effects at the portal of entry (e.g., nasal cancer) or systemic effects (e.g., leukemia) when stating:

> *The toxicokinetic knowledge and the exposure route will be considered in the context of whether effects occur at the portal of entry or systemically.*

Since the NAS (2011) review, more definitive data on the lack of systemic distribution of inhaled formaldehyde have become available (Lu et al., 2011; Moeller et al. 2011; Edrissi et al. 2013, 2017; Yu et al. 2015; Lai et al., 2016; Leng et al., 2019). It is noteworthy that the more recently published peer-reviewed literature provides further support for the conclusions reached by the NAS (2011) that there is a lack of causal evidence Such evidence on causality, or the lack thereof, was recently assessed by

Gentry et al. (2020) using the IPCS MOA framework. They concluded that LHPs are highly unlikely to be directly related to inhalation of formaldehyde.

NAS (2011), development of dose-response criteria, further stated:

> *EPA used studies of the National Cancer Institute (NCI) cohort of U.S. workers exposed to formaldehyde through its production or its use (Hauptmann et al. 200412; Beane-Freeman et al. 200913) to estimate unit risk values for three cancers—nasopharyngeal cancer, Hodgkin lymphoma, and leukemia. The committee agrees that the NCI studies are a reasonable choice because they are the only ones with exposure and dose-response data sufficient for calculation of the unit risks; however, the studies are not without their weaknesses, which should be clearly discussed and addressed in the revised IRIS assessment. Although there are uncertainties as discussed above regarding the causal relationship of formaldehyde exposure and the three kinds of cancer, EPA's decision to calculate unit risk values for them appears to be defensible on the basis of the agency's cancer guidelines. However, EPA should provide a clear description of the criteria that it used to select the specific cancers and demonstrate a systematic application of the criteria. The calculation of the unit risk values is a complex process, involves many sources of uncertainty and variability, and is influenced by the low-dose extrapolation used (for example, linear vs threshold). The committee therefore recommends that EPA conduct an independent analysis of the dose-response models to confirm the degree to which the models fit the data appropriately. EPA is encouraged to consider the use of alternative extrapolation models for the analysis of the cancer data; this is especially important given the use of a single study, the inconsistencies in the exposure measures, and the uncertainties associated with the selected cancers.*

And

> *EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohematopoietic cancers. Experimental evidence of either mechanism is lacking.*

And

> *Revisit arguments that support determinations of causality of specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to the conclusions.*

The Draft Assessment still considers indirect biomarkers of systemic genotoxicity as evidence supporting a genotoxic MOA. The Draft Assessment uses this mechanism to support the hypothesis of cytogenetic effects in circulating blood cells and calculate a linear IUR for leukemia in the absence of any dose-response observations for leukemia or demonstration of in vivo genotoxicity. The approach taken in the Draft Assessment clearly does not follow or adequately address the NAS comments above.

2. AN INCOMPLETE SYSTEMATIC REVIEW CALLS INTO QUESTION THE FOUNDATION OF CONCLUSIONS REACHED IN THE DRAFT ASSESSMENT

Systematic review requires using a systematic method to summarize evidence on questions with a detailed and comprehensive plan of study. It includes literature searching, grading of confidence for studies, and evaluation of papers in an objective manner. The IRIS Draft fails to satisfy the requirements of systematic review.

Example 1: A critically deficient systematic review of the literature was performed

The systematic review of literature contained in the Draft Assessment was inadequate. The Draft Assessment itself verifies that the systematic review was bifurcated and rushed, and that simple literature searches were performed pre-2017 and post-2017, as stated:

> *A series of comprehensive literature searches was conducted beginning in 2012 and updated annually through 2016, after which the completed 2017 Step 1 draft IRIS formaldehyde-inhalation assessment was suspended at the request of senior EPA management. When the IRIS assessment was unsuspended in March 2021 (http://www.epa.gov/sites/production/files/2021-03/documents/iris_program_outlook_mar2021.pdf), systematic evidence mapping (SEM) methods ("Template Systematic Evidence Map (SEM): Report Format and Methods Used for the US EPA Integrated Risk Information System (IRIS) Program, Provisional Peer Reviewed Toxicity Value (PPRTV) Program, and Other "Fit for Purpose" Literature-Based Human Health Analyses [submitted July 2021]) were employed to survey the newer literature and expedite updating the unsuspended draft* [underlining added for emphasis]

The above indicates that, against EPA policy, a full systematic review of the literature was not conducted before release of the Draft Assessment for peer-review. Also, inadequate and incomplete science cannot be justified by a desire to "expedite" an update to a 12 year old draft document. This deficiency must be addressed before any further revisions are initiated.

Example 2: Due to a deficient systematic review, information that was, or should have been, known to the Administrator was excluded from the Draft Assessment.

As stated in the EPA (2021) draft IRIS Staff Handbook:

> *"A broad, preliminary literature survey is typically carried out to identify health effects or types of toxicity that have been studied in conjunction with exposure to the chemical or substance as well as key toxicokinetic and mode-of-action (MOA) issues"*

However, as described in Table 1 (p. xxiv), and as stated in the Draft Assessment (p. xxv): MOA studies were not included in the search strategy:

> *...relevant literature on additional topics (e.g., formaldehyde exposure, toxicokinetics, mechanisms of carcinogenesis) was identified. While a thorough effort was made to identify all*

relevant studies for each of these topic areas (see Appendix A for details), these discussions do not include specific tracking of the selection of individual studies (e.g., based on PECO criteria).

And (p. xxvii of preface),

Individual study evaluations for literature on exposure, toxicokinetics and other mechanistic data were not systematically conducted and documented.

Not including MOA studies in the literature search or in the PECO statement directly conflicts with EPA guidance.

Example 3: There are numerous studies that should have been evaluated in the Draft Assessment, but were not cited or referenced

EPA has excluded or dismissed a number of key studies, reviews, responses, and presentations, with a majority having been presented in correspondence and presentations by the ACC Formaldehyde Panel to the Agency since 2011.

Important studies, reviews, or responses which are not referenced in the external review draft for EPA's toxicological review (789 pp) or supplemental information (1058 pp):[1]

Albertini, R.J. and Kaden, D.A., 2017. Do chromosome changes in blood cells implicate formaldehyde as a leukemogen?. *Critical Reviews in Toxicology*, *47*(2), pp.145-184.

Allegra, A., Spatari, G., Mattioli, S., Curti, S., Innao, V., Ettari, R., Allegra, A.G., Giorgianni, C., Gangemi, S. and Musolino, C., 2019. Formaldehyde exposure and acute myeloid leukemia: a review of the literature. *Medicina*, *55*(10), p.638.

Andersen, M.E., Gentry, P.R., Swenberg, J.A., Mundt, K.A., White, K.W., Thompson, C., Bus, J., Sherman, J.H., Greim, H., Bolt, H. and Marsh, G.M., 2019. Considerations for refining the risk assessment process for formaldehyde: Results from an interdisciplinary workshop. *Regulatory Toxicology and Pharmacology*, *106*, pp.210-223.

Bachand, A.M., Mundt, K.A., Mundt, D.J. and Montgomery, R.R., 2010. Epidemiological studies of formaldehyde exposure and risk of leukemia and nasopharyngeal cancer: a meta-analysis. *Critical reviews in toxicology*, *40*(2), pp.85-100.*

Bosetti, C., McLaughlin, J.K., Tarone, R.E., Pira, E. and La Vecchia, C., 2008. Formaldehyde and cancer risk: a quantitative review of cohort studies through 2006. Annals of Oncology, 19(1), pp.29-43.*

[1] * denotes studies, reviews, or responses referenced in supplemental information but not the main text; ** denotes studies, review, or responses briefly referenced in the main text but not the supplemental information.

Casanova, M., Cole, P., Collins, J.J., Conolly, R., Delzell, E., Heck, H.D.A., Leonard, R., Lewis, R., Marsh, G.M., Ott, M.G. and Sorahan, T., 2004. Re: Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *Journal of the National Cancer Institute*, *96*(12), pp.966-967.

Catalani, S., Donato, F., Madeo, E., Apostoli, P., De Palma, G., Pira, E., Mundt, K.A. and Boffetta, P., 2019. Occupational exposure to formaldehyde and risk of non hodgkin lymphoma: a meta-analysis. *BMC cancer*, *19*(1), pp.1-9.

Chang, E.T., Ye, W., Zeng, Y.X. and Adami, H.O., 2021. The evolving epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiology and Prevention Biomarkers*, *30*(6), pp.1035-1047.

Checkoway, H., Boffetta, P., Mundt, D.J. and Mundt, K.A., 2012. Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. *Cancer Causes & Control*, *23*(11), pp.1747-1766.

Checkoway, H., Lees, P.S., Dell, L.D., Gentry, P.R. and Mundt, K.A., 2019. Peak exposures in epidemiologic studies and cancer risks: considerations for regulatory risk assessment. *Risk Analysis*, *39*(7), pp.1441-1464.

Cole, P., Adami, H.O., Trichopoulos, D. and Mandel, J., 2010. Formaldehyde and lymphohematopoietic cancers: a review of two recent studies. *Regulatory Toxicology and Pharmacology*, *58*(2), pp.161-166.

Cole, P., Adami, H.O., Trichopoulos, D. and Mandel, J.S., 2010. Re: Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. Journal of the National Cancer Institute, 102(19), pp.1518-1519.

Cole, P. and Axten, C., 2004. Formaldehyde and leukemia: an improbable causal relationship. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.107-112.

Collins, J.J. and Lineker, G.A., 2004. A review and meta-analysis of formaldehyde exposure and leukemia. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.81-91.*

Collins, J.J., Ness, R., Tyl, R.W., Krivanek, N., Esmen, N.A. and Hall, T.A., 2001. A review of adverse pregnancy outcomes and formaldehyde exposure in human and animal studies. *Regulatory Toxicology and Pharmacology*, *34*(1), pp.17-34.

Collins, J.J., Esmen, N.A. and Hall, T.A., 2001. A review and meta-analysis of formaldehyde exposure and pancreatic cancer. *American journal of industrial medicine*, *39*(3), pp.336-345.*

European Food Safety Authority, 2014. Endogenous formaldehyde turnover in humans compared with exogenous contribution from food sources. *EFSA Journal*, *12*(2), p.3550.

Gaylor, D.W., Lutz, W.K. and Conolly, R.B., 2004. Statistical analysis of nonmonotonic dose-response relationships: Research design and analysis of nasal cell proliferation in rats exposed to formaldehyde. *Toxicological Sciences*, *77*(1), pp.158-164.

Gentry, R., Thompson, C.M., Franzen, A., Salley, J., Albertini, R., Lu, K. and Greene, T., 2020. Using mechanistic information to support evidence integration and synthesis: a case study with inhaled formaldehyde and leukemia. *Critical reviews in toxicology*, *50*(10), pp.885-918.

Golden, R., 2011. Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. *Critical reviews in toxicology*, *41*(8), pp.672-721.

Golden, R. and Holm, S., 2017. Indoor air quality and asthma: has unrecognized exposure to acrolein confounded results of previous studies?. *Dose-Response*, *15*(1), p.1559325817691159.

Golden, R. and Valentini, M., 2014. Formaldehyde and methylene glycol equivalence: critical assessment of chemical and toxicological aspects. *Regulatory Toxicology and Pharmacology*, *69*(2), pp.178-186.

Golden, R., Pyatt, D. and Shields, P.G., 2006. Formaldehyde as a potential human leukemogen: an assessment of biological plausibility. *Critical reviews in toxicology*, *36*(2), pp.135-153.

Hartwig, A., Arand, M., Epe, B., Guth, S., Jahnke, G., Lampen, A., Martus, H.J., Monien, B., Rietjens, I.M., Schmitz-Spanke, S. and Schriever-Schwemmer, G., 2020. Mode of action-based risk assessment of genotoxic carcinogens. *Archives of toxicology*, *94*(6), pp.1787-1877.

Heck, H.D.A. and Casanova, M., 2004. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regulatory Toxicology and Pharmacology*, *40*(2), pp.92-106.**

Just, W., Zeller, J., Riegert, C. and Speit, G., 2011. Genetic polymorphisms in the formaldehyde dehydrogenase gene and their biological significance. *Toxicology letters*, *207*(2), pp.121-127.

Lu, K., Hsiao, Y.C., Liu, C.W., Schoeny, R., Gentry, R. and Starr, T.B., 2021. A Review of Stable Isotope Labeling and Mass Spectrometry Methods to Distinguish Exogenous from Endogenous DNA Adducts and Improve Dose–Response Assessments. *Chemical Research in Toxicology*.

Lu, K., Ye, W., Zhou, L., Collins, L.B., Chen, X., Gold, A., Ball, L.M. and Swenberg, J.A., 2010. Structural characterization of formaldehyde-induced cross-links between amino acids and deoxynucleosides and their oligomers. *Journal of the American Chemical Society*, *132*(10), pp.3388-3399.**

Lu, K., Ye, W., Gold, A., Ball, L.M. and Swenberg, J.A., 2009. Formation of S-[1-(N 2-deoxyguanosinyl) methyl] glutathione between glutathione and DNA induced by formaldehyde. *Journal of the American Chemical Society*, *131*(10), pp.3414-3415.

Marsh, G.M., Morfeld, P., Zimmerman, S.D., Liu, Y. and Balmert, L.C., 2016. An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study. *Journal of Occupational Medicine and Toxicology*, *11*(1), pp.1-15.*

Marsh, G.M., Morfeld, P., Collins, J.J. and Symons, J.M., 2014. Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. *Journal of Occupational Medicine and Toxicology*, *9*(1), pp.1-9.

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Mundt, K.A., Gentry, P.R., Dell, L.D., Rodricks, J.V. and Boffetta, P., 2018. Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity. *Regulatory Toxicology and Pharmacology*, *92*, pp.472-490.

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[2] Included in main text references but not in text nor in appendices.

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Pyatt, D., Natelson, E. and Golden, R., 2008. Is inhalation exposure to formaldehyde a biologically plausible cause of lymphohematopoietic malignancies?. *Regulatory Toxicology and Pharmacology*, *51*(1), pp.119-133.

Rhomberg, L.R., Bailey, L.A., Goodman, J.E., Hamade, A.K. and Mayfield, D., 2011. Is exposure to formaldehyde in air causally associated with leukemia?—A hypothesis-based weight-of-evidence analysis. *Critical Reviews in Toxicology*, *41*(7), pp.555-621.

Rhomberg, L.R., 2015. Contrasting directions and directives on hazard identification for formaldehyde carcinogenicity. *Regulatory Toxicology and Pharmacology*, *73*(3), pp.829-833.

Speit, G., Heinz-Peter, G., Pallapies, D. and Morfeld, P., 2010. Occupational Exposure to Formaldehyde, Hematotoxicity and Leukemia-Specific Chromosome Changes in Cultured Myeloid Progenitor Cells-Letter (vol 19, pg 1882, 2010). *Cancer Epidemiology Biomarkers and Prevention*, *19*, pp.2991-2991.

Starr, T.B. and Swenberg, J.A., 2014. Response to Crump et al. *Regulatory toxicology and pharmacology: RTP*, *70*(3), pp.737-738.

Starr, T.B. and Swenberg, J.A., 2013. A novel bottom-up approach to bounding low-dose human cancer risks from chemical exposures. *Regulatory Toxicology and Pharmacology*, *65*(3), pp.311-315.**

Tarone, R.E. and McLaughlin, J.K., 2005. Re:"mortality from solid cancers among workers in formaldehyde industries". *American journal of epidemiology*, *161*(11), pp.1089-1090.

Thompson, C.M., Gentry, R., Fitch, S., Lu, K. and Clewell, H.J., 2020. An updated mode of action and human relevance framework evaluation for Formaldehyde-Related nasal tumors. *Critical reviews in toxicology*, *50*(10), pp.919-952.

Thompson, C.M., 2018. Commentary on new formaldehyde studies in Trp53 haploinsufficient mice: further support for nonlinear risks from inhaled formaldehyde. *Dose-Response*, *16*(2), p.1559325818777931.

Van Landingham, C., Mundt, K.A., Allen, B.C. and Gentry, P.R., 2016. The need for transparency and reproducibility in documenting values for regulatory decision making and evaluating causality: The example of formaldehyde. *Regulatory Toxicology and Pharmacology*, *81*, pp.512-521.

Wolkoff, P. and Nielsen, G.D., 2010. Non-cancer effects of formaldehyde and relevance for setting an indoor air guideline. *Environment international*, *36*(7), pp.788-799.

Zeller, J., Högel, J., Linsenmeyer, R., Teller, C. and Speit, G., 2012. Investigations of potential susceptibility toward formaldehyde-induced genotoxicity. *Archives of toxicology*, *86*(9), pp.1465-1473.

Zeller, J., Ulrich, A., Mueller, J.U., Riegert, C., Neuss, S., Bruckner, T., Triebig, G. and Speit, G., 2011. Is individual nasal sensitivity related to cellular metabolism of formaldehyde and susceptibility towards formaldehyde-induced genotoxicity?. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *723*(1), pp.11-17.

In addition, several important studies and reviews, while briefly cited by EPA in the main text of the assessment, are summarily dismissed by the Agency (in several cases devoting a sentence or less, or a single footnote to the content). Examples include:

Gentry, P.R., Rodricks, J.V., Turnbull, D., Bachand, A., Van Landingham, C., Shipp, A.M., Albertini, R.J. and Irons, R., 2013. Formaldehyde exposure and leukemia: critical review and reevaluation of the results from a study that is the focus for evidence of biological plausibility. *Critical reviews in toxicology*, *43*(8), pp.661-670.

Lu, K., Boysen, G., Gao, L., Collins, L.B. and Swenberg, J.A., 2008. Formaldehyde-induced histone modifications in vitro. *Chemical research in toxicology*, *21*(8), pp.1586-1593.

Mundt, K.A., Gallagher, A.E., Dell, L.D., Natelson, E.A., Boffetta, P. and Gentry, P.R., 2017. Does occupational exposure to formaldehyde cause hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells?. *Critical Reviews in Toxicology*, *47*(7), pp.598-608.

3. THE DRAFT ASSESSMENT INHIBITS THE REVIEWERS ABILITY TO SEPARATE SUBJECTIVITY FROM OBJECTIVITY IN THE CONCLUSIONS REACHED

Example 1: The Draft Assessment frequently uses subjective terms such as "low" and "high" with variable definition and often without definition. This obfuscates conclusions and reduces understanding how quantitative exposure – response relationships are characterized.

For example, on page 2-10 of the dose response analysis, the IRIS draft states *"..formaldehyde concentrations were high, imposing substantial uncertainty regarding responses at the low tail of the exposure distribution."* No explanation of "low exposure" is provided. This is particularly concerning, as "low exposure" likely refers to levels equivalent to an average exposure in homes (Salthammer T. 2019. Formaldehyde sources, formaldehyde concentrations and air exchange rates in European housing. Building and Environment 150: 219–232) with median concentrations ranging from 12 – 39 μm^3. Subjective language is used throughout the Draft Assessment. For illustrative purposes, Table 1 presents air concentrations that were accompanied by a measure of what was meant by "low" and "high" concentrations, when the concentrations were defined, and Table 2 presents some examples where the use of the subjective terms obscures interpretation of the results. In particular for terms dealing with exposure it is best to define "low", etc. using criteria established at the outset of the analysis.

Table 1: Frequent use of subjective terms such as "low" and "high" with changing definition

Draft Assessment Terminology	Concentration Identified	Citation Page
Low		
low concentrations	(e.g., 0.25–0.3 mg/m^3) in humans	Overview, p. 70
low concentrations	2 ppb to 18 ppb	p. 1-3
low concentrations	>0.666, maximum 0.444 mg/m^3	p. 1-30
low concentrations	≥0.3 mg/m^3	p. 1-310
High/Higher		
	≥11 mg/m^3 in rats and 9 mg/m^3 in mice	p. 1-154
	Rats >10 mg/m^3	p. 1-155
	Rats >12 mg/m^3	p. 1-337
	Highly exposed occupational population 0.222-2.91 mg/m^3	p. 1-413

	High exposure concentrations 3.6 ppm and 4.5 ppm	p. 2-73
Excessive		
	≥20 mg/m^3	p. 1-136
	>7 mg/m^3	p. 1-360
Narrow range		
	<0.005 mg/m^3	p. xxv of preface

Table 2: Use of subjective terms such as "low" and "high" without definition

Draft Assessment Terminology	Concentration or Magnitude Identified	Citation Page
Slightly		p. 2-77
The benchmark response was extended slightly below the observed range?	None	
Low		
Uncertainties remain regarding the relative impact of duration on the development of hyperplasia .... particularly at low formaldehyde levels	None	
via transient receptor potential channel stimulation at low concentrations	N The claim by Marsh et al. (2007b; 2002) suggests a one-sided uncertainty The claim by Marsh et al. (2007b; 2002) suggests a one-sided uncertainty one	p. 1-514
at low concentrations but progressed to more distal parts of the nose (cross-section Levels II–V) at higher concentrations	None	p. 2-17
Moderate		
. . . potential for lesions in the larynx and trachea of rats at sustained high formaldehyde concentrations and in rhesus monkeys at sustained moderate concentrations	None	1-150
. . . following exposure to relatively high concentrations, with similar results in Wistar or Sprague Dawley rats, although occasionally necrosis is reported at more moderate exposure levels.	None	1-296

following acute, discontinuous, or moderate concentration exposure scenarios	None	3-117
therefore does not transport directly to the systemic blood circulation at moderate exposure concentrations	None	p. 1-6
at low-to-moderate exposure levels that elicit marginal increases in frank tissue toxicity	None	p. 1-294
to relatively high concentrations, with similar results in Wistar or Sprague Dawley rats, although occasionally necrosis is reported at more moderate exposure levels.	None	p. 1-296
High		
with high concentrations of formaldehyde distributed to squamous, transitional, and respiratory epithelium	None	p. 1-3
In rats exposed by inhalation to high concentrations of formaldehyde, a rapid GSH depletion can occur,	None	p. 1-9
asthmatic volunteers consistently did not observe changes, even at high concentrations,	None	p. 1-33
Reduction in pulmonary function was observed across several different exposure settings, all involving high formaldehyde exposure.	None	p. 1-45
a lower level of confidence would be applied to high concentration studies	None	Overview p. 90
Pathological indications of significant epithelial necrosis in F344 rats are primarily reported following exposure to relatively high concentrations,	None	p. 1-296
Preterm birth and low birth weight were not associated with higher formaldehyde exposures.	None	p. 1-412
extremely high concentrations expected to cause strong irritant effects	None	p. 1-416
A large variety of occupations were included within the studies; some represented work settings with a high likelihood of exposure to high levels of formaldehyde.	None	p. 1-421, 1-422

The frequent and inconsistent use of subjective terms, results in an overly complicated Draft Assessment that is confusing and difficult to interpret. As shown in Table 1, the term "low concentration" can range from about 0.002 to 0.4 mg/m^3, "high concentration" from about 3 to >12 mg/m^3, and "excessive concentrations from about 7 to ≥20 mg/m^3, the overlapping and ill defined subjective terms makes interpretation of statements such as those highlighted in Table 2 almost impossible to put into context. The level of subjectivity in the language used in the Draft Assessment must be reduced to increase transparency in study interpretations.

Example 2: There are many instances of language supporting a subjectively predetermined outcome.

The Draft Assessment routinely uses language that is used to support a predetermined conclusion. The following provides some examples of the subjective tone used throughout the Draft Assessment:

Draft Assessment Quotation	Citation Page	Alternative
The claim by Marsh et al. (2007b; 2002) **suggests** a one-sided uncertainty in the exposure-response reported by Beane Freeman et al. (2013)	1-198	Marsh et al. (2007b; 2002) reported a one-sided uncertainty in the exposure-response reported by Beane Freeman et al. (2013)
Marsh et al. (2007b) **suggests that** silversmithing may be a cause of NPC and that the reported association between formaldehyde and NPC may be due to confounding.	1-209	Marsh et al. (2007b) **cited literature that** silversmithing is correlated with NPC and that the reported association between formaldehyde and NPC may be due to confounding.
. . . two strains of p53 deficient mice failed to observe any treatment-related increases in nasal tumors at 32 weeks post-exposure, despite pronounced metaplasia (NTP, 2017). Additional study using longer-term exposures, ideally in rat models (as mice are demonstrably less sensitive), **would help clarify the role** of p53 in URT carcinogenesis.	1-305.	. . . two strains of *p53* deficient mice failed to observe any treatment-related increases in nasal tumors at 32 weeks post-exposure, despite pronounced metaplasia (NTP, 2017). Additional study using longer-term exposures, ideally rat models (as mice are demonstrably less sensitive), would help **clarify if there is a role** of p53 in URT carcinogenesis. (new text bolded)
Overall, **evidence is emerging** that formaldehyde exposure may pose a hazard for ALS	1-332	Overall, **evidence is insufficient to conclude** that formaldehyde exposure may pose a hazard for ALS, and this endpoint is not carried forward for hazard identification or dose-response assessment
The potential for developmental neuropathology remains a significant concern.	1-341	Overall, **evidence is insufficient to conclude** that formaldehyde exposure may pose a neuropathological hazard, and this endpoint is not carried forward for hazard identification or dose-response assessment
Overall, the data indicate the potential for an effect, but the evidence is insufficient to conclude that formaldehyde exposure causes neural excitation or acts a proconvulsant.	1-344	~~Overall, the data indicate the potential for an effect, but~~ The evidence is insufficient to conclude that formaldehyde exposure causes neural excitation or acts a proconvulsant
Available human evidence is interpreted as *slight* … As no experimental animal or mechanistic studies specific to this effect were identified (i.e., indeterminate), overall the **evidence suggests** that formaldehyde inhalation might cause the fatal human disease, ALS, but additional study is needed for stronger judgement.	1-359	Available human evidence is interpreted as *slight* … As no experimental animal or mechanistic studies specific to this effect were identified (i.e., indeterminate), and formaldehyde is not systemically distributed, overall **evidence inadequate** that formaldehyde inhalation might cause ~~the fatal human disease~~, ALS~~, but .a.~~ Additional study ~~is needed for stronger judgement~~ would be helpful to clarify the indeterminant dataset.

While mechanisms for the induction of myeloid leukemia and multiple myeloma **are yet to be elucidated**, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.	p. 1-418	**Potential mechanisms** for the induction of myeloid leukemia and multiple myeloma **have not been elucidated**. However, if formaldehyde is causal, the mechanism does not involve direct interactions between formaldehyde and bone marrow constituents, as it is not distributed beyond the nasal passages at relevant exposure levels (i.e., ≤15 ppm). As such, any causal association must be via an indirect mechanism related to point-of-contact toxicity, which is adequately protected against by exposure standards set below levels that results in upper respiratory tract toxicity.
A study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases that are expected to yield effect estimates that **underestimate** any true effect.	p. 1-421	A study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases that are expected to yield effect estimates that underestimate **or overestimate** any true effect.
Other evidence supportive of the development of these cancers (e.g., hematological changes) is discussed in the Evidence on Mode of Action for Lymphohematopoietic Cancers Section.	p. 192	Other evidence **supportive and not supportive of** the development of these cancers (e.g., hematological changes) is discussed in the Evidence on Mode of Action for Lymphohematopoietic Cancers Section.
Although the two other available **studies failed to observe statistically significant**, treatment-related increased in LHP cancers in potentially sensitive mice (NTP, 2017) or rats (Sellakumar et al., 1985) . . .	p. 1-194	**The two other available studies did not identify any statistically significant** of biologically relevant increased in LHP cancers in potentially sensitive mice (NTP, 2017) or rats (Sellakumar et al., 1985).
Taken together**, it appears that mechanisms yet to be elucidated** that do not involve direct interactions of formaldehyde in the bone marrow **need to be considered**	p. 1-540	Taken together, **the evidence does not support any plausible way** in which inhaled formaldehyde can cause leukemia without being systemically distributed.
The fact that the two-sided p-values are not strictly <0.05 is not critical here, given that the hazard for NPC was established a priori in Chapter 1	p. 2-48	**The incidence for NPC was not statistically significant** for any of the exposure groups relied upon when developing the inhalation unit risk factor, with p values of 0.1, 0.16 and 0.07 for peak, average and cumulative exposures, respectively (Table 2-15).

Example 3: The criteria for inclusion/exclusion of studies published after 2017 are unclear. The Draft Assessment gives the appearance of subjectively excluding evaluation of any studies that did not impact conclusions made before 2017, in confidential internal review drafts that remain unavailable to the public and were not externally peer-reviewed.

As stated in the Draft Assessment (p. xxv):

> *Most notably, after screening the studies for PECO relevance, only those studies meeting the PECO criteria and judged as likely to have a potential impact on the conclusions or toxicity values described in the suspended 2017 draft are synthesized in this assessment.*

Potential impact is not defined, nor are criteria given. Excluding studies that do not impact conclusions made in a confidential internal draft assessment inappropriately limits the range of science considered and impedes a full and objective assessment of the literature.

Example 4: EPA selectively contacted some authors of peer-reviewed literature to seek clarification on study details and results, in order to improve the reliability score for those studies. Other study authors were not contacted, subjectively influencing the quality rankings for published studies.

As stated in the Draft Assessment (p. xxvii):

> *In some situations, in which key study details or results were not presented, the study author(s) were contacted to obtain this information. Any additional study details obtained from the authors are noted in the evaluation summary tables and evidence tables.*

Example 5: The Draft Assessment subjectively over weights the affirmative/positive conclusion of adversity, as the assessment's review of the literature is always considered to underestimate adverse effects. The potential for overestimating adversity is not considered.

In the main text of the Draft Assessment "bias toward the null" is identified 155 times. No other form of bias was ever identified. This demonstrates that the Draft Assessment only considered the potential for underestimating adversity and risks. There is not a single reference to the possibility that studies and/or the Draft Assessment itself may be biased toward the affirmative/positive. Furthermore, there is no discussion of publication bias. This is particularly problematic, because publication bias toward positive results in epidemiology studies is well known, and there are many peer-reviewed publications on this specific form of bias (e.g., Siddiqi, N. 2011. Publication Bias in Epidemiological Studies. Cent Eur J Public Health 2011, 19(2):**118-**120). This should be recognized in any further drafts of the IRIS formaldehyde assessment.

Example 6: Subjective exclusion of "evidence against" (not supporting) the conclusions reached in the Draft Assessment is contradictory to EPA guidelines

As stated in the EPA (2001) IRIS Handbook:

An understanding of mechanistic pathways (e.g., by identifying mechanistic precursor events linked qualitatively or quantitatively to apical health effect[s]) can influence the strength of the evidence integration conclusions, providing either support for or against biological plausibility

And,

"The integration of evidence involves narrative summaries that bring together the findings from the analyses of the informative evidence relevant to each potential human health hazard, including summary judgments regarding the strength of the evidence (for or against an effect) from each evidence stream and as a whole (aka, a weight-of-evidence analysis of the totality of evidence). During evidence integration, a set of factors describing aspects of the evidence (e.g., consistency; dose-response) is evaluated for each assessed hazard using structured frameworks and predefined considerations across the sets of relevant studies (both positive and null). These evaluations of the available studies of exposed humans and experimental animals inform interpretations about the extent to which the data support a judgment that a human health hazard exists (or is unlikely to exist)"

The Draft Assessment also outlines the key consideration for evidence integration conclusions, with Step 1 being Integration of Health Effect and Mechanistic Evidence in Humans or Animals and Step 2 being Evidence Integration Conclusions, which states (p. xxxxvii):

The judgments regarding the human and animal evidence are integrated in light of evidence on the human relevance of the findings in animals, susceptibility, and the coherence of the findings across evidence streams to draw a conclusion about the evidence for health effects in humans.

The Draft Assessment, however, sets aside both animal and mechanistic information and solely calculates Reference Concentrations (RfCs) and Inhalation Unit Risks (IURs) based on individual study results. Toxicokinetic, dosimetry, animal, and mechanistic data are not integrated into the assessment of epidemiology results when calculating exposure limits/IURs, when they appear to contradict numerically identified associations from epidemiology.

Example 7: The Assessment's frequent uses of the words assume, assuming, and assumption indicates the conclusions were based on assumptions, rather than the evidence

The Draft Assessment makes frequent use of the words, as follows:

- "Assume" is used 74 times in the Summary Information document
- "Assuming" is used 23 times in the Summary Information docu The Assessment's frequent uses of the words assume, assuming, and assumption indicates the conclusions were based on assumptions, rather than the evidence ment
- "Assumption" is used 44 times in Summary Information document

For a total of 144 instances.

We note that use of assumptions and defaults is often needed in proceeding with an assessment. However, this approach is generally required for data-poor chemicals and is not

appropriate for extremely well-studied chemicals such as formaldehyde. The overuse of these terms gives strong support to the conclusion that the Draft Assessment is more default or assumption driven than driven by the evidence. Hopefully, this will be addressed in any future drafts of the IRIS formaldehyde assessment.

4. THE EXPERIMENTAL ANIMAL EVIDENCE IS OFTEN INAPPROPRIATLY REJECTED OR DOWN GRADED DUE TO MISINTERPRETATIONS

Example 1: The experimental evidence in animals on formaldehyde inhalation was incorrectly assessed in the Draft Assessment, leading to an inaccurate determination that *"the evidence available from animal studies is considered indeterminate for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma."*

Formaldehyde is one of the most-studied chemicals in the world. Reflecting this, eleven cancer bioassays have been performed with formaldehyde (that have recently been reviewed by Thompson et al., 2020), via the inhalation route: seven in rats, two in mice, and two in hamsters. A complete animal experimental database in laboratory animals is often considered to consist of chronic bioassays in two species, which clearly formaldehyde exceeds. If the formaldehyde cancer bioassay database is considered indeterminate, then virtually no experimental database can meet the bar set in the Draft Assessment. We disagree with the low rating of the overall study quality of the database in the Draft Assessment. Notably the Draft Assessment rated one rat cancer study (Table 1-65) and one mouse cancer study as "high confidence" studies, clearly meeting the EPA definition of a complete database for assessing formaldehyde carcinogenicity. Thus, it is unclear why his database was considered "indeterminant" in the Draft Assessment. Neither of the two high confidence studies identified a treatment-related increase in leukemia; their exclusion from integration into the assessment of leukemogenic potential prevents the Draft's conclusions from reflecting best available science.

After rating the Battelle (1982) mice and rat studies with "High Confidence" (Table 1-65), as appropriate, the text inexplicably states:

> *Given the paucity of available information and difficulties interpreting the Battelle (Battelle, 1982 results, the evidence available from animal studies is considered indeterminate for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma.*

Additional statements on the Battelle (1982) study seem to justify a predetermined conclusion. Examples from the Draft Assessment:

1) *As stated in the Draft Assessment (p. 1-512),*

> *At the intermediate dose groups of 2.5 mg/m^3 and 6.9 mg/m^3 exposure concentrations, only the target (i.e., the nasal passages) tissues were examined unless unusual tissue masses or gross lesions were noted, or if the animals died spontaneously, and the study report does not provide incidence at these doses in their summary findings (Battelle, 1982).*
>
> We find the characterization of the pathology in the Battelle (1982) study to be incorrect and misleading as to tissue examination. As stated in Kerns (1983) which was a peer-reviewed summary of the Battelle (1982) study:

All major tissues from each organ system (approximately 50 tissues/animal) in the control and high exposure groups were evaluated histologically.

This Draft Assessment quote implies that reading of the slides was done incorrectly when it was not. The pathology practice of only "reading" the high dose slides and not evaluating the intermediate dose groups, when no effects were seen in the high dose groups, merely reflects standard practice to "read down" as defined by the EPA (OPPTS 870.4300), as there is little need to evaluate lower dose groups if the high dose group showed no effects (i.e., no dose-response would be realized).

2) As stated in the Draft Assessment (p. 1-493),

> *"survival rates for rats were decreased by formaldehyde exposure at the 17.6 mg/m^3 exposure for males and females. For the mice, there was no differential mortality across exposure groups; however there appeared to be decreased survival in all exposure groups after 6 months."*

The quote implies an incorrect procedure, and there was none. As stated in EPA guidelines (OPPTS 870.4300):

> *For a meaningful and valid statistical evaluation of long term exposure and for a valid interpretation of negative results, the number of animals in any group should not fall below 50 percent at 15 months in mice and 18 months in rats. Survival in any group should not fall below 25 percent at 18 months in mice and 24 months in rats.*

This guidance is not only for statistical evaluation, which was not compromised, but also to avoid excessive toxicity confounding interpretation of results as being directly related to the test substance or a secondary effect of dosing above toxicokinetic thresholds. Excess mortality and toxicity are known to cause cancer via indirect mechanisms, not directly to the test substance, and excess mortality shifts bias toward the positive/affirmative, which was not the case for leukemia in the rat and mouse studies.

Considering these comments, we disagree with the conclusion made in the Draft Assessment (p. 1-493);

> *"It is problematic to infer from these results because of the lack of information at the intermediate dose groups and the adverse effect on survival."*

This conclusion likely led to unjustified conclusions being made regarding low quality and reliability of the available cancer bioassays.

EPA (2005) Cancer Risk Assessment guidelines state:

> *The high dose in long-term studies is generally selected to provide the maximum ability to detect treatment-related carcinogenic effects while not compromising the outcome of the study through excessive toxicity or inducing inappropriate toxicokinetics (e.g., overwhelming absorption or detoxification mechanisms).*

<u>Example 2: The experimental evidence in animals is incorrectly assessed in the Draft Assessment, leading to an inaccurate determination that "the evidence available from animal studies is considered indeterminate for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma."</u>

Statistical associations are simple numerical differences which are often not causal, reflect random variability, and should not be overinterpreted

The Draft Assessment (p. 1-493) states:

*There was a suggestion of a **possible increased** incidence in lymphoma (p-value, 0.06) in female mice, and a **decreased incidence in leukemia in female rats (p-value, 0.006)** at the high dose. The **possible increase** in lymphoma incidence in mice is of interest for future study [bold and color added for emphasis]*

And,

It is also difficult to interpret the apparent slight increase in lymphoma in mice alongside the slight but statistically significant decrease in leukemia in female rats.

These statements, again, reflect the need to evaluate all lines of evidence when making a hazard identification determination. In any large study there will be random variations in observations, hence the need for both statistical analysis and consideration of the biology. There is little reason to give great weight to a non-statistically significant increase in the numbers of animals with lymphoma (not leukemia). Given that there is an abundance of information demonstrating that inhaled formaldehyde is not systemically distributed, the biological relevance of this non-significant increase is not supported. Secondly, it should not be assumed that the statistically significantly decreased leukemia incidence in the high dose group demonstrates that formaldehyde inhibits cancer, including reduction of the background incidence of rat leukemias. Since inhaled formaldehyde is not systemically distributed, it should simply be considered as natural variation. This is not *"difficult to interpret"* as stated on p. 1-493 of the Draft Assessment.

Moreover, the negative results for leukemia in high confidence studies in rats and mice were supported by medium and low confidence studies, as described in the Draft Assessment (p. 1-494).

The USEPA Cancer Risk Assessment Guidelines (2005) also state:

Moreover, the absence of tumors in well-conducted, long-term animal studies in at least two species provides reasonable assurance that an agent may not be a carcinogenic concern for humans.

And,

Studies of the absorption, distribution, biotransformation, and excretion of agents permit comparisons among species to assist in determining the implications of animal responses for human hazard assessment, supporting identification of active metabolites, identifying changes in distribution and metabolic pathway or pathways over a dose range, and making comparisons among different routes of exposure.

If extensive data are available (e.g., blood/tissue partition coefficients and pertinent physiological parameters of the species of interest), physiologically based toxicokinetic models can be constructed to assist in a determination of tissue dosimetry, species-to-species extrapolation of dose, and route-to-route extrapolation (Conolly and Andersen, 1991; see Section 3.1.2). If sufficient data are not available, it may be assumed as a default that toxicokinetic and

metabolic processes are qualitatively comparable among species. Discussion of appropriate procedures for quantitative, interspecies comparisons appears in Chapter 3.

The qualitative question of whether an agent is absorbed by a particular route of exposure is important for weight of evidence classification, discussed in Section 2.5. Decisions about whether route of exposure is a limiting factor on expression of any hazard, e.g., absorption does not occur by a specified route, are generally based on studies in which effects of the agent or its structural analogues have been observed by different routes, on physical-chemical properties, or on toxicokinetics studies. Adequate metabolism and toxicokinetic data can be applied toward the following, as data permit.

Confidence in conclusions is enhanced when in vivo data are available

Highly reliable *in vivo* toxicokinetic information is available that conclusively demonstrates that inhaled formaldehyde is not systemically distributed at ≤15 ppm and, thus, cannot directly result in leukemia at concentrations near or below current exposure limits (e.g., OSHA PEL of 0.75 ppm)
And, as stated in EPA Cancer Risk Assessment Guidelines (p. 2-57),

In other cases, there can be convincing evidence in both humans and animals that the agent is not carcinogenic. The judgment may be based on data such as:

• animal evidence that demonstrates lack of carcinogenic effect in both sexes in well designed and well-conducted studies in at least two appropriate animal species (in the absence of other animal or human data suggesting a potential for cancer effects),

• convincing evidence that carcinogenic effects are not likely by a particular exposure route (see Section 2.3), or

• convincing evidence that carcinogenic effects are not likely below a defined dose range

There is highly reliable and convincing experimental evidence in cancer bioassays that inhaled formaldehyde does not cause leukemia, is not systemically distributed, and cannot directly cause any systemic effects via inhalation. This evidence should not be graded *"indeterminate"* for drawing conclusions in any subsequent drafts of the IRIS Formaldehyde Assessment. By contrast, the epidemiology study used to derive the draft inhalation unit risk factor did not show a statistically significant increase incidence of myeloid leukemia and should not be used to justify finding a causal association.

The grading of these "high confidence" studies as "indeterminate" leads to a final conclusion that is not supported by the evidence. As stated in the Draft Assessments conclusions (p. 1-522):

Thus, there appears to be a lack of support for the human epidemiological evidence from rodent bioassays, although concordance across species is not necessarily expected (U.S. EPA, 2005a). The apparent lack of consistency in results raises uncertainties about the currently available research results on these diseases, including how formaldehyde exposure-induced LHP cancers might arise without substantial distribution to target sites. Notably, the available animal evidence was judged as indeterminate and not compelling evidence of no effect (see assessment Preface), as there are important uncertainties that prevent such an interpretation. Thus, the animal evidence does not detract from the strength of the association between formaldehyde

exposure and myeloid leukemia (and related mechanistic changes) in epidemiology studies [Emphasis added].

The Draft Assessment's evaluation of the animal evidence contained numerous errors and contradictions that resulted in grading the evidence being judged as indeterminate, despite High Confidence cancer studies in both rats and mice, supported by medium and low confidence studies demonstrating the lack of leukemogenic potential in animals. Dismissing "high confidence" studies as "indeterminate" and not considering them as evidence while classifying a numerical association in epidemiological studies as causal (particularly when the findings were not even statistically significant) during evidence integration is bad science and is specifically prohibited by EPA guidance. This must be corrected in any future drafts of the IRIS formaldehyde assessment.

Example 3: The Draft Assessment often relies on animal studies performed with novel and unvalidated test methods to reach conclusions.

As an example, as described further in these peer-review comments, each of the animal studies relied upon for developing organ specific reference concentrations (osRfCs) in the Draft Assessment, relied on novel methods, such as measuring seminiferous tubule diameter, without providing any hematoxylin and eosin (H&E) stained tissue section histopathological evaluation by a trained pathologist, or measuring metal concentrations in lungs or testes without even providing critical information such as body weights, food consumption, hematology, clinical signs, sufficient number of animals for statistical evaluation, etc. as is expected of any well conducted toxicology study using validated endpoints for assessing toxicity.

Example 4: Strength and weight of the evidence determinations in animal studies are often subjective, unfounded, and contradictory

It is troublesome for the Draft Assessment to conclude both the Ozen et al. 2002 and 2005 publications are "high" reliability but then state (p. 87) that: *"Confidence in the database is also considered low because, while a number of published studies evaluated reproductive toxicity in males, the interpretation of study results is complicated by their methodological limitation and excludes use of formaldehyde concentrations above 6 mg/m^3, and data are lacking regarding functional endpoints."*

This sort of disparity in confidence levels (i.e., High Reliability of the two studies used to derive the RfC, but low confidence in the database) must be addressed in any future revisions to the Draft Assessment.

5. The DRAFT ASSESSMENT DID NOT CONSIDER TOXICOKINETICS IN EITHER HAZARD IDENTIFICATION OR DOSE RESPONSE ASSESSMENT AND FAILS TO ACKNOWLEDGE THE LACK OF SYSTEMIC DISTRIBUTION OF INHALED FORMALDEHYDE IN AN INTEGRATED MANNER.

Example 1: The Draft Assessment presents RfCs for a number of non-cancer systemic effects, including reproductive/developmental effects in females and reproductive toxicity in males, despite the fact that NAS (2011) previously identified this as problematic and not supported by the evidence.

When addressing the practice of calculating a formaldehyde RfC, based on systemic effects, the NAS (2011) stated:

> *...formaldehyde is absorbed primarily at the site of first contact where it undergoes extensive local metabolism and reactions with macromolecules. Thus, the net result is that inhaled formaldehyde remains predominantly in the respiratory epithelium that lines the airways. The committee concludes that the weight of evidence suggests that formaldehyde is unlikely to appear in blood as an intact molecule except perhaps at concentrations high enough to transiently overwhelm the metabolic capability of the tissue at the site of exposure. Thus, direct evidence of systemic delivery of formaldehyde is generally lacking.*

Since the NAS (2011 review), numerous studies have conclusively demonstrated that inhaled formaldehyde is not systemically circulated through the blood or other systems. Furthermore, there is now direct molecular dosimetry evidence that, at concentrations below 15 ppm, there is no detectable systemic delivery of inhaled formaldehyde, at detection limits over a thousand times lower than endogenous levels of formaldehyde. The Draft Assessment, however, fails to take this evidence into account and incorporate the recommendations of the NAS (2011) peer-review by developing RfCs for reproductive and developmental effects (Table 2-10) that rely on the assumption of systemic delivery of inhaled formaldehyde.
NAS (2011) indicated that at environmentally relevant concentrations, some systemic effects could be elicited, to reproductive organs, if the exposure was via the oral route, but not the inhalation route:

> *A major concern in connection with developmental and reproductive toxicity is whether formaldehyde can penetrate past the portal of entry. That critical question affects the conclusions drawn from the animal studies, particularly those in which exposure was by a route other than inhalation.*

And,

> *When given by oral exposure or by injection, formaldehyde or its metabolites are capable of reaching reproductive tissues and the fetus. However, whether inhaled formaldehyde passes the portal of entry to access distant tissues—such as the gonads, hypothalamus, or the fetus—remains unresolved.*

A decade ago, before more recent and definitive toxicokinetic data was available, the NAS (2011) stated:

> *Heck et al. (1985) did not observe an increase in blood formaldehyde concentrations in rats and humans after exposure to inhaled formaldehyde at 14.4 ppm (2 hr) or 1.9 ppm (40 min), respectively. Subchronic studies conducted in rhesus monkeys have also shown that blood formaldehyde concentration was not measurably altered by exposure to airborne formaldehyde at 6 ppm for 6 hr/day 5 days/week for 4 weeks (Casanova-Schmitz et al. 1984).*

The NAS (2011) also noted:

> *The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation, particularly at sites beyond the respiratory tract.*

And

Despite species differences in uptake due to differences in breathing patterns and nasal structures, formaldehyde is absorbed primarily at the site of first contact where it undergoes extensive local metabolism and reactions with macromolecules. Thus, the net result is that inhaled formaldehyde remains predominantly in the respiratory epithelium that lines the airways.

And

The committee concludes that the weight of evidence suggests that formaldehyde is unlikely to appear in the blood as an intact molecule except perhaps at concentrations high enough to transiently overwhelm the metabolic capability of the tissue at the site of exposure. Thus, direct evidence of systemic delivery of formaldehyde is generally lacking.

And

In fact, additional data based on even more sensitive analytic methods published since the draft assessment was released casts further doubt on the hypothesis that formaldehyde reaches the systemic distribution in a form that can react with macromolecules in tissues remote from the portal of entry (Lu et al. 2011; Moeller et al. 2011; Swenberg et al. 2011).

Additional biomarker of exposure/molecular dosimetry studies since the time of these NAS (2011) statements and conclusions have only strengthened the weight-of-evidence on formaldehyde binding and/or detoxification at the portal of entry. Newer studies continue to contribute to the evidence demonstrating concentrations of formaldehyde in air that are ≤15 ppm result in no detectable systemic distribution of inhaled formaldehyde (Edrissi et al., 2013; Lai et al., 2016; Leng et al., 2019).

Example 2: The Draft Assessment assumes inhaled formaldehyde acts via an unknown pathway to cause cytogenic effects in blood cells, mutagenic effects in systemically circulating blood cells, and suggest a mutagenic MOA for systemic effects, despite NAS (2011) critiques of this approach

When addressing cytogenetic effects in blood, purportedly supporting a mutagenic MOA for leukemia, the NAS (2011) stated:

...the Committee concludes that data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. First the observed effects have occurred in highly exposed people and extrapolating to more typical environmental exposure is difficult given the uncertainty surrounding the form of the dose-response curve for cytogenetic changes. Second, a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established. That gap in mechanistic understanding is particularly problematic because the data strongly suggest that formaldehyde is not available systemically in any reactive form.

Over the last four decades, toxicokinetic and toxicodynamic studies have consistently demonstrated a lack of systemic distribution of inhaled formaldehyde concentrations up to 15-20 ppm when directly measured in tissues (Heck et al., 1985; Casanova et al., 1988). More recent publications quantified protein and DNA biomarkers of formaldehyde exposure confirming that there is no systemic distribution of formaldehyde air concentrations ≤15 ppm (Lu et al. 2010, 2011; Edrissi et al. 2013, 2017; Yu et al. 2015; Lai et al. 2016; Leng et al. 2019).

In addressing immunotoxicity the NAS and EPA (2010) were in agreement:

> *The committee agrees with EPA's decision to not calculate a candidate RfC on the basis of immunotoxicity studies.*

The Draft Assessment did not consider the human cytogenicity observations as relevant to calculating an RfC. The Draft Assessment, however, considered the same questionable observations as sufficient evidence to conclude there is reliable evidence of cytogenicity (and therefore mutagenicity) in systemically circulating blood cells in humans. This inconsistency when evaluating the same study is not scientifically reported is not good science.

More pointedly the NAS (2011) also stated:

> *The draft IRIS assessment correctly concludes that formaldehyde is a genotoxic (DNA-reactive) chemical that causes cytogenetic effects, such as mutations. Furthermore, the overall body of evidence suggests that inhaled formaldehyde has a cytogenetic effect that can be detected in peripheral (circulating) blood lymphocytes. However, the committee concludes that data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. First, the observed effects have occurred in highly exposed people, and extrapolating to more typical environmental exposures is difficult given the uncertainty surrounding the form of the dose-response curve for cytogenetic changes. Second, a mechanism that would explain the occurrence of cytogenetic effects in circulating blood cells has not been established. That gap in mechanistic understanding is particularly problematic because the data strongly suggest that formaldehyde is not available systemically in any reactive form. Thus, the committee can only hypothesize that the observed effects result from an unproven mechanism in portal-of-entry tissues.*

The Draft Assessment maintains problematic conclusions on systemic genotoxicity/mutagenicity in circulating blood cells. The Draft Assessment continues to conclude that a mutagenic MOA is operable for systemic effects, despite conclusive evidence that formaldehyde is not systemically distributed after inhalation, at environmentally relevant concentrations. It is hard to understand why the EPA continues to conclude that a potential biomarker of a mutagenic effect on circulating blood cells, that is not dose-responsive, supports a linear low-dose leukemogenic response, when EPA has previously and repeatedly been advised this approach is problematic.

6. THE DRAFT ASSESSMENT DOES NOT INTEGRATE DOSIMETRY INTO ANALYSIS SUPPORTING HAZARD IDENTIFICATION OR DOSE RESPONSE AND DOES NOT ACCOUNT FOR ENDOGENOUS PRODUCTION OF FORMALDEHYDE AND THE HOMEOSTATIC STATE IN NORMAL INDIVIDUALS.

Example 1: The Draft Assessment does not attempt to integrate dosimetry into the quantitative analysis of risk. Rather it describes a hypothesis on how an external exposure - that is orders of magnitude less than the amount of formaldehyde generated through endogenous metabolism - can upset homeostasis or drive any systemic biological process.

The Draft Assessment concludes that an understanding of homeostasis is not important when considering if there is added risk from exogenous exposure to formaldehyde. However, it is critical to

understand the normal role of formaldehyde in the body, such as its central role in one carbon metabolism when determining adversity. The Draft Assessment also speculates that inhaled formaldehyde is somehow different than endogenously produced formaldehyde, an assumption that challenges our basic understanding of chemistry. Formaldehyde is a simple molecule; it is simply formaldehyde and should not be assessed differently or separately, depending on whether it is generated in the body or derived from an external source. As stated in the Draft Assessment (Preface, p. li):

> *Once formaldehyde is inhaled and interacts with extracellular aqueous matrices such as mucus in nasal passages and is hydrated, the biochemical reactivity of inhaled formaldehyde and endogenous formaldehyde are likely to be very similar, given that there are no differences in chemical structure. However, no specific data are available to inform whether there may be differences in interactions with specific extracellular or intracellular macromolecular targets in vivo. While the rate of cellular detoxification of exogenous formaldehyde remains unknown, the production and subsequent detoxification of endogenous formaldehyde appears to be kept under strict control and has been well described (Burgos-Barragan et al., 2017b).* [underlining for emphasis added]
>
> *Although understanding of the contribution of endogenous formaldehyde levels on health is minimal, the Toxicological Review assumed that these impacts on background incidence of prevalence of cancer or other health hazards were accounted for because the focus of the assessment is to estimate the extra risk that results from exogenous exposure over background risk. Endogenous formaldehyde might be responsible for some portion of background risks for some health outcomes, particularly when normal detoxification pathways are deficient (e.g., Pontel et al., 2015); but that possibility is not the purpose of this review. [underlining for emphasis added].*

First, exogenous and endogenous formaldehyde are not similar -- they are identical. Claiming that there are no specific data indicating that they are different implies a conclusion that is not correct. While there are no data indicating that they are different, there is overwhelming evidence that formaldehyde is simply formaldehyde, regardless of where it is found or how it is generated. Secondly, stating that *"the rate of cellular detoxification of exogenous formaldehyde remains unknown"* ignores the wealth of data on the half-life of formaldehyde *in vivo* and its non-specific binding to electrophilic centers, as well as an abundance of data on the kinetics of detoxification by glutathione and aldehyde dehydrogenase. Thirdly, one of the best characterized metabolic pathways is the one-carbon pathway that includes detoxification of formaldehyde by formaldehyde dehydrogenase (ADH5/GSNOR). Stating that *"our understanding the contribution of endogenous formaldehyde is minimal"* ignores the extensive database demonstrating that formaldehyde is an essential anabolic building block needed for normal metabolism. Simply, one cannot live in the absence of formaldehyde. Ignoring the essentiality of formaldehyde and the equivalence of formaldehyde regardless of its origin is a fundamental flaw of the Draft Assessment. When in a state of homeostasis, there is no added risk. As such, assessing added risk in the context of homeostasis must be a critical component of the Draft Assessment and must not be put aside.

Key to understanding and managing exogenous inhaled formaldehyde is that at concentrations that do not upset normal variability (i.e., ≤1-2 ppm) in metabolic processes, there is no added risk. The Draft

Assessment must be revised to integrate relative dosimetry and define concentrations at which inhaled formaldehyde does not upset normal homeostasis.

This topic was also the focus of the "bottom up" approach published by Drs. Swenberg, Starr and Lu in several peer-reviewed publications, which were incorrectly characterized in the Draft Assessment.

Example 2: Reproductive Effects at Maternally Toxic Concentrations were Incorrectly Determined to Represent a Hazard for Classification Purposes

The Draft Assessment incorrectly concludes that "evidence indicates" that inhalation of formaldehyde causes increased risk of reproductive and developmental toxicity, and classifies it as a reproductive and development hazard. This is despite the statement (p. 1-414) that *"The primary basis for this conclusion is based on bioassays in rodents testing formaldehyde concentrations above 6 mg/m^3."* In drawing this conclusion, the Draft Assessment excludes both toxicokinetic considerations and relative dosimetry. This is in direct opposition to Globally Harmonized Classification and Labeling (GHS) guidance as well as EPA guidance on evaluating reproductive and developmental toxicity. First, inhaled formaldehyde is not distributed systemically, thus, it does not affect normal formaldehyde concentrations in reproductive or developmental organs/systems, so it cannot be a direct hazard. Secondly, any reproductive effects were only observed under conditions of high toxicity in the dams, which does not trigger a Hazard Classification for reproductive effects, according to EPA guidelines or GHS. As such, it must not be classified as presenting a reproductive and developmental hazard.

This incorrect classification also results in an unfounded call for additional animal testing to evaluate these endpoints, in direct conflict with EPA policy and TSCA law that unnecessary animal use must be avoided whenever possible. As stated (p. 1-414):

> *The findings by Wang et al. (2015) suggesting formaldehyde-related toxicity to sperm and possible resulting effects on fecundity and fetal survival, and which may be supported by a low confidence study in mice (Xing et al., 2007), provide evidence of male-mediated decreases in fetal viability, and should be investigated further. Ideally, such investigations would include additional human studies of different populations using similarly detailed exposure assessments, as well as single or multigeneration reproductive toxicity studies in animals (which were not identified in the current database). Such studies would also assess female reproductive outcomes, which are not extensively evaluated in the current database. [Emphasis added]*

At levels not resulting in maternal toxicity inhaled formaldehyde is not distributed systemically and is detected only at quantities thousands of times lower than the naturally occurring background concentrations of endogenous formaldehyde. Any effects on reproduction and development can only occur at maternally toxic formaldehyde concentrations and be due to indirect effects resulting from that toxicity. Single and multigenerational studies would result in the unnecessary use of thousands of laboratory animals to evaluate effects that can only be directly related to maternal toxicity. Thus, effects that do not reflect a chemical-specific effect should not warrant further evaluation.

Example 3: Endogenous formaldehyde and homeostasis are inappropriately ignored in the Draft Assessment of nasal tumor risk, resulting in unsupported use of linear extrapolation of risk.

Dr. Chad Thompson personally briefed the EPA on his publication [Thompson et al. (2020). Crit Rev. Toxicol 50(10), p. 919-952]; however, the manuscript was not cited in the Draft Assessment. Besides

summarizing the DNA and protein adduct work that conclusively demonstrates no detectable dosimetry to nasal epithelial DNA at concentrations ≤0.3 ppm, the authors summarized toxicokinetics and identified the concentrations of inhaled formaldehyde that result in exogenous exposures exceeding endogenous levels of formaldehyde in the nasal epithelium:

> *Based on measured formaldehyde concentrations, it is estimated that mammals produce between 0.61 and 0.91 mg of formaldehyde per kilogram bodyweight per minute (EFSA 2014). Assuming an average of 0.76 mg/kg bodyweight formaldehyde production per minute, a 250 g rat produces over 1000 mg/kg-day[4] or 274 mg/day. Based on nasal tissue volume estimates of 200 mm^3 (equating to 200 mg)[5] (Gross et al. 1982), the nasal compartment would contribute 0.08% to this total formaldehyde production, or 0.22mg of formaldehyde per day (274 mg/day 0.08%). Assuming 100% deposition of formaldehyde into the nasal tissue region, the inhalation concentrations used in formaldehyde cancer bioassays result in estimated tissue doses that exceed endogenous levels (i.e. 0.22 mg) starting somewhere between 2 and 6 ppm (Table 2).*
>
> *Consistent with this exceedance between 2 and 6 ppm, Andersen et al. (2010) developed a pharmacokinetic model linking inhaled formaldehyde exposures (input) to loss through exhalation, diffusion, reversible GSH binding and metabolism to formate, as well as crosslinking based on earlier data on ^{14}C-DNA-protein crosslinks (discussed in the following section). Andersen et al. (2010) model predictions indicated that exposure to 2 ppm would result in minimal changes in GSH and formaldehyde acetal formation, whereas exposures above 4 ppm depletes GSH more rapidly with concomitant increases in formaldehyde acetal formation.*

Concordance of effects and other information that supports a threshold MOA, supported by dosimetry was excluded from the assessment. Understanding that the nasal tumors form only at exposure levels at which normal homeostasis has been upset is a critical point in apprehending why a threshold is observed in tumor response. These data argue strongly against the use of low dose linear extrapolation into the zone of homeostasis (below background levels of endogenously produced formaldehyde).

Example 4: The Draft Assessment does not appropriately integrate the molecular dosimetry and toxicokinetic information into the evaluation of cause and effect for leukemia

For leukemia dose response assessment, the Draft Assessment uses several methods, both for deriving the inhalation unit risk (IUR) factor for myeloid leukemia and for different combinations of myeloid leukemia and other types of leukemia. Each of the derived IURs, presented in Tables 2-31 through 2-25 fall within the range of 0.03 to 0.48 (per mg/m3). No mention of relative dosimetry related to naturally occurring background concentrations of formaldehyde is included in the assessment of uncertainties in Table 2-36 or included in the section (2.2.5) of the draft assessment that was titled *"Cancer Risk Based on "Background Cancer Incidence and Internal Dose of Endogenous and Exogenous Formaldehyde."*

The erroneous results of not assessing the added exposure, yet evaluating added risk, are exemplified by a comparison the exogenous exposure at 0.1 mg/m^3, (which is the WHO Indoor Air Quality Guideline [IAQG]) to the normal endogenous exposure. At an exposure concentration of 0.1 mg/m^3 and an inhalation rate of 20 mg/m^3, the amount of formaldehyde inhaled is 2 mg/person. In contrast, the amount of formaldehyde generated endogenously ranges from 61,460 - 91,700 mg/person/day (EFSA, 2014). At the WHO IAQG, the amount of formaldehyde that is inhaled is between 30,730 to 45,850 times less than that normally present in the body. This calculation is supported by numerous molecular

dosimetry studies that demonstrate there are no exogenous DNA or protein adducts in systemic tissues, including blood, at exposure concentrations up to 15 mg/m^3, against a high background concentration of endogenous adducts in systemic tissues, including blood.

It is hard to envision a situation where 1/30,000th (i.e., 0.003%) of the exposure/dose can drive any biological process, much less present an unreasonable risk. However, the Draft Assessment concludes that *"There are insufficient data to establish the MOA(s) for formaldehyde-induced myeloid leukemia; thus, linear low-dose extrapolation was performed as the default approach."*

It seems that an alternative approach would be to recognize that there are considerable uncertainties in the Draft Assessment cancer risk estimates, that there is direct evidence against an association between leukemia and formaldehyde at environmentally relevant concentrations, and that the associations between formaldehyde and myeloid leukemia were not statistically significant in the study used to calculate the IUR.

The Draft Assessment states, *"The cumulative exposure metric also yielded nearly statistically significant exposure-response relationships (p = 0.07) and was used for the cancer risk calculations in this assessment" [Emphasis added].* This is by contrast to a more direct statement that the results were not statistically significant at p≤0.05.

No valid, scientific assessment would consider a metric as being "nearly statistically significant." A metric is either statistically significant or it is not. If it's not, then it cannot be used as evidence of a relationship, without other supporting data, which in this case argue against causality (e.g., no effect in animal studies, toxicokinetic information demonstrating lack of systemic distribution, relative dosimetry).

The Draft Assessment further says that EPA *"...used an innovative approach to derive and present a potential unit risk estimate for myeloid leukemia."*). However, it is more likely that there is no increased risk of leukemia at exposures/doses that do not add substantially to naturally occurring levels of formaldehyde in the body. This interpretation was recently reached by both the WHO and the European Chemicals Agency. Excluding this interpretation from consideration is not scientifically supportable.

This topic was also the focus of the "bottom up" approach published by Drs. Swenberg, Starr and Lu in several peer-reviewed publications, which was incorrectly characterized in the Draft Assessment

7. THE DRAFT ASSESSMENT DOES NOT INCORPORATE ALL LINES OF EVIDENCE INTO HAZARD IDENTIFICATION

The Draft Assessment does not integrate evidence on exogenous vs. endogenous formaldehyde exposure, nor does it utilize information on toxicokinetics when completing hazard characterization. Several specific examples regarding the failure of the Draft Assessment to adhere to the EPA guidelines related to data integration are as follows:

Example 1: The Draft Assessment dismisses well-established toxicokinetic information found in the published literature in favor of multiple, hypothetical, assumptions.

The Draft Assessment preface (p. xxi) states:

Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the upper respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde. [underlining added for emphasis]

Furthermore, the Draft Assessment (footnote p. xxi), states:

Note that none of the health effects evaluated in this assessment approached the level of evidence need to support a judgment of strong evidence supports no effect, so this level is not discussed.

Data from multiple sources provide strong evidence that formaldehyde is not systemically distributed and, therefore, could not directly cause any systemic effect. The Draft Assessment assumes that formaldehyde acts via an unknown pathway to elicit systemic effects (e.g., female reproductive or developmental toxicity, male reproductive toxicity, nervous system toxicity, and leukemia).

Example 2: Studies that according to USEPA guidance are unreliable should have been excluded from the determination of hazard and/or dose-response, but they were often inappropriately considered relevant and integrated into conclusions.

The text below describes the selection of studies that impact both hazard identification and dose response assessments.

As stated in the Draft Assessment (introduction, pages XXX – XXXi) and applicable to **both** epidemiology and laboratory animal studies:

"...methanol could result in differences in tissue-specific formaldehyde levels at identical external formaldehyde exposure levels when different test articles are used. This limitation typically introduces a bias toward an effect and is of particular concern in studies observing systemic effects after exposure. Thus, the test article used to generate the formaldehyde atmosphere in experimental studies was critically evaluated (see Appendix A.5 for details), including consideration of whether a methanol-only control group was used.[3] Although this evaluation was applied to all experimental systems, conclusions about the level of uncertainty introduced by this coexposure varied by health outcome, with a far greater level of concern for potential impacts on nonrespiratory health effects (see Section 1.3, Nervous System Effects, developmental and reproductive system effects, and lymphohematopoietic (LHP) cancers), as compared to respiratory health effects (see Section 1.2). This disproportionate level of concern is primarily based on two factors: (1) as compared to formaldehyde, which does not appear to be distributed to distal sites in appreciable amounts, inhaled methanol would be readily transported beyond the portal of entry (POE) and could elicit direct effects at distal target tissues, and (2) certain

systemic effects evaluated in this assessment (i.e., reproductive and developmental toxicity, nervous system effects) are health outcomes known to be a target of methanol toxicity,"

The draft IRIS Staff Handbook (2021; pg. 6-3) states the following regarding study confidence ratings:

> *"Uninformative: An unacceptable study where serious flaw(s) make the study results unusable for informing hazard identification. Studies with critically deficient judgments in any evaluation domain will almost always be classified as uninformative (see explanation above). Studies with multiple deficient judgments across domains may also be considered uninformative. Uninformative studies will not be considered further in the synthesis and integration of hazard identification or dose-response but may be used to highlight possible research gaps"*

A critically deficient evaluation domain for the assessment of formaldehyde is methanol co-exposure. Any study (epidemiological or animal) with methanol co-exposure should generally be classified as uninformative rather than "low confidence" when related to systemic effects. The Draft Assessment overstates in their conclusions "...the evidence indicates that inhalation of formaldehyde likely causes increased risk of xxx" for studies that were confounded by methanol.

Example 3: Neurotoxicity and reproductive and developmental toxicity studies used for dose-response and/or hazard classification did not meet the criteria in USEPA guidance for the confidence ratings proposed in the Draft Assessment yet were advanced (sometimes even all of the way to RfC development).

Male Reproductive Toxicity Studies that were Critically Deficient in Numerous Domains were Inappropriately Advanced in the Draft Assessment:

The Ozen et al. (2002) and Ozen et al. (2005) subchronic rat studies were rated "high confidence" studies and used to derive osRfCs for potential male reproductive toxicity in the Draft Assessment. Both studies had numerous deficiencies that would lead to a grade of "uninformative" and thus not used for either hazard classification or dose-response assessment, as follows.

Ozen et al. (2002)

Ozen et al. (2002) was rated high confidence (p. 1-369; p. 1-402) in the Draft Assessment. Two formaldehyde concentrations of 12.2 and 24.4 mg/L were stated in the abstract to have been tested, although that unit of exposure was in error and later changed by errata to 12.2 and 24.4 mg/m^3. Seven male rats per dose group and a control were exposed for two different time periods (4-week and 13-week periods), 8 hr/day, 5 days/wk. Only three measurements were taken during the study: body weights, testes weights, and quantification of metals in testes (limited to Zn, Cu, Fe). The lowest concentration tested of 12.4 mg/m^3 was identified as the LOAEL. The Draft Assessment applied exposure duration adjustment and a combined uncertainty factor of 3000 to derive a cRfC of 0.001. The study was also used to support a hazard classification of "evidence indicates [likely]" a male reproductive toxicant (see Table 1, page 2, overview doc).

Critical deficiencies in the study include the following:

1. The study did not follow any recognized guidelines for performing toxicology studies.

2. The study did not include an appropriate number of animals. EPA guidelines for subchronic toxicity testing require 10 animals/group (not 7), and EPA guidelines for reproduction and developmental testing require either 10 or 25 rats/group (EPA/630/R-96/009; OPPTS 870.3465; OPPTS 3550; OPPTS 3650; OPPTS 3700; OPPTS 3800).

3. The study did not include an appropriate number of dose groups (only two rather than the three required by EPA guidelines for subchronic and reproductive and developmental toxicity testing (EPA/630/R-96/009; OPPTS 870.3465; OPPTS 3550; OPPTS 3650; OPPTS 3700; OPPTS 3800).

4. There was incomplete reporting of data in the study.

    a. Body weight and testes weights were not reported, but rather only body weight gains and relative testes weights. As recognized in the Draft Assessment this is a critical deficiency: *"Insufficient information (on either the mean testes or body weights used in deriving the relative weight values) was provided in Özen et al. (2002)."*

    b. There was inconsistent reporting of Özen et al. (2002), wherein the distinction between decreased testes weights and decreased relative testes weights was also noted, further obscuring the actual reporting of the results from this study. As stated on p. 1-414 *"while significantly decreased dose- and duration-dependent testes weights were observed in the high confidence study in rats by Özen et al. (2002).*

    c. No clinical data were reported, although it was clear that excessive systemic toxicity was noted in all study groups (see b.w. gain below, as well as indications of excessive toxicity reported at similar concentrations in a similar study reported by Ozen et al (2005))

5. Body weight gains indicated excessive toxicity in both dose groups, obscuring any assessment of a direct reproductive effect on the testes. Body weight gain decreases between 58% and 87% were reported for each treatment group, which are well above the Maximum Tolerated Dose (MTD) that is generally recognized as body weight gain decreases ≥10%. The Draft Assessment concludes *"The confidence in the POD derived from its results is low, given that the lowest formaldehyde concentration tested in this study was 12 mg/m^3"* [page 87], but conclude that the study itself is a "high confidence" study. The Draft Assessment presented a similar claim for another study conducted by the same group (Ozen et al., 2003), p. A-618): *"Not informative (overt toxicity; endpoint protocol description insufficient" and* based on this deficiency the Draft Assessment rated Ozen (2003) "low confidence." This highlights the major inconsistencies in the way the Draft Assessment assigned quality ratings for different studies, sometimes even as similarly reported by the same author, or perhaps even the same study reported in two different manuscripts.

6. There was no dose-response observed for decreased testes weights.

7. Changes in metal concentrations in testes are of unknown toxicological significance, as these measurements have not been validated as predictive of a toxicological effect. This was

recognized in the Draft Assessment (p. 87) as a deficiency: *"... the interpretation of study results is complicated by their methodological limitations ....and data are lacking regarding functional endpoints."* Furthermore, it is striking that in the assessment of metal concentrations measured in the lungs of rats after subchronic inhalation, reported by the same author (Ozen et al. 2003), the Draft Assessment (p. A-456-457) states *"Note: unclear relevance of endpoints: authors claim Fe change linked to oxidative stress and Zn change linked to decreased DNA synthesis, but no direct evidence"*. The Draft Assessment was inconsistent in applying a rating of low confidence to Ozen et al. (2003) while rating the Ozen et al. (2002) study as having "High Confidence."

8. Even when "results" were reported, the original data were not. The "results" of relative to body weight reported were not the EPA preferred metric. As stated in the Draft Assessment (p. 86, overview), on reporting only relative testes weights: *" absolute organ weights are preferred for this measure"*.

Applying EPA guidance and considering these eight major study deficiencies in Ozen et al. (2002), this study should have been rated "indeterminate" or "not informative" and not carried forward for either hazard assessment or dose-response analysis.

Ozen et al. (2005)

In a subchronic toxicity study (Ozen et al., 2005) exposed male rats (6/group) to air concentrations of 0, 5 or 10 ppm formaldehyde generated from paraformaldehyde. Exposures were for 8 hr/day, 5 days/wk over a 91 day period. Results for only four endpoints were reported: 1) mean seminiferous tubule diameters from 100 randomly selected tubules/group; 2) immunohistochemical staining for Hsp70 content in testicular tissue; 3) mean terminal testosterone serum levels; and 4) clinical signs. Statistically significant changes in mean seminiferous tubule diameters were observed in both dose groups, a semi-quantitative assessment indicated increased staining for Hsp 70 content in spermatocytes and spermatids, a statistically significant 6–9% decrease in serum testosterone (T) was observed, and severe clinical signs were reported

It is noteworthy that the quality rankings for this study are inconsistent within the Draft Assessment. For example, Ozen (2005) was ranked as "high confidence" in one sentence on p 1-396 and "medium confidence" in another sentence on the same page.

Critical deficiencies in the study include:

1 The study did not follow any recognized guideline for performing subchronic toxicology studies (e.g., OPPTS 3465, OECD 413).

2 Neither the endpoint of increased Hsp70 in spermatids and spermatocytes, nor the diameter of seminiferous tubules has been validated as either predictive measures of adverse effects or as adverse effects themselves. Additionally, quantitation of serum T concentrations has not been established as a reliable predictor of adverse effects, although these measures may indicate a potential hazard in a well-conducted study.

3 The study did not include an appropriate number of animals. EPA guidelines for subchronic toxicity testing require 10 animals/group (not 6)(OPPTS 3465), and EPA guidelines for

reproduction and developmental testing require either 10 or 25 rats/group (testing (EPA/630/R-96/009; OPPTS 870.3465; OPPTS 3550; OPPTS 3650; OPPTS 3700; OPPTS 3800), while this study used only 6 animals/group.

4 The study did not include an appropriate number of dose groups (only two as opposed to the three required by EPA guidelines for subchronic and reproductive and developmental toxicity testing.

5 There was incomplete reporting of data in the study

i. It was clear that excessive systemic toxicity was noted in the two treatment groups: see body weight (B.W.) gain below, as well as indications of excessive toxicity reported at similar concentrations in a similar study reported by Ozen et al (2005).

ii. The method for measuring seminiferous tubules was not described, and it is impossible to determine how many animals were assessed for testes changes; the paper reports only that 100 seminiferous tubules/group were assessed. As stated in the Draft Assessment (Page 2-6, Table 2-1) *"Unclear usefulness of data for quantification: for example, as the results reflect randomly selected tubules, the tubules could be oversampled from individual animals within a group, and the mean and variability across the group of animals when using the animal as the experimental unit is unknown."* Also, stated in the Draft assessment summary (p. 84) *"Analysis of pooled tissues; interpretability to individual rats uncertain"*. We find that to be an understatement, as no information regarding how tissues were assessed was provided in the manuscript.

6 There was no reporting of body weights or organ weights.

7 The inhalation exposures were whole body, rather than nose only. Significant confounding can result from whole body exposures. This is particularly troublesome for the assessment of systemic effects, as secondary oral exposures occurs from licking of fur. In the Ozen et al. (2005) study, it is probable that significant confounding for systemic effects from secondary exposures occurred, as it was reported that: *"the fur of rats exposed to 10 ppm of FA turned yellow on the tenth day of exposure."*

8 There was overt toxicity in this study, which is a major confounder when assessing systemic toxicity. As reported (Ozen, 2005): *"In addition, unsteady breathing, an increase in nose cleaning, excessive licking, frequent sneezes and hemorrhage in the nasal mucosa were observed because of FA irritation."* These effects clearly reflect excessive toxicity, as defined by EPA. For example, the EPA Cancer Risk Assessment Guidelines state: *"an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10%), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology."* In addition, food and water consumption was relatively decreased in the treated groups. Clearly, the animals in this study were overdosed at concentrations above the MTD. This deficiency was highlighted in the Draft Assessment for a different study conducted by the same group (Ozen et al., 2003) (p. A-618): *"Not informative (overt toxicity; endpoint protocol description insufficient". The* Draft Assessment used this

deficiency to rate Ozen et al. (2003) "low confidence." This variation highlights major inconsistencies in the way the Draft Assessment assigned quality ratings for different studies, sometimes even as similarly reported by the same author. Ozen et al. (2005) was rated "high confidence", and Ozen et al., (2003) was rated as "low confidence."

9 There was no dose-response observed for seminiferous tubule diameter decreases, as both dose groups had essentially the same seminiferous tubule diameters (236 versus vs. 233 μM).

10 There was no indication in the study report that the exposures levels were confirmed analytically.

According to USEPA guidelines and considering numerous and critical deficiencies clearly identified in the Ozen et al. (2005) study, the Draft Assessment should have classified the study as "Uninformative" rather than "high confidence". The study was inappropriately used in hazard characterization (i.e., Evidence indicates (likely) male reproductive toxicity) and dose-response assessment (i.e., calculation of an cRfC of 0.0002 mg/m^3.

Even if these studies were deemed to be free from other critical deficiencies, Ozen et al. (2002) and (2005) studies should not have be used for hazard characterization for male reproductive toxicity, due to the reported excessive toxicity; that is both marked reduction in B.W. gain and severe clinical signs). As stated in EPA (1996) Guidelines for Reproductive Toxicity Assessment:

> *In the presence of severe body weight depression or other severe systemic debilitation, it should be noted that an adverse effect on a reproductive endpoint occurred, but the effect may have resulted from a more generalized toxic effect.*

Considering the dramatic decline in body weight gain in the treatment groups, any effects observed were likely secondary to the occurrence of nonreproductive toxicity and not directly related to the test article.

Developmental Neurotoxicity

EPA Guidelines for Reproductive and Development Toxicity say the following:

> *Impairment that is secondary to more generalized physical debilitation (e.g., impaired rear leg motor activity or general lethargy) should not be considered an adverse reproductive effect, although such conditions represent adverse systemic effects.*

On page 1-360, the Draft Assessment reached this conclusion:

> *Data from experimental animal studies also suggest that excessive formaldehyde inhalation (levels >7 mg3) may cause developmental neurotoxicity. The evidence most informative to this potential health effect was a medium confidence study (i.e., two publications on the same experiment) examining neuropathological changes in rats"*

Note that this is actually one study that was split into three publications. The Draft Assessment Table 1-46 (p. 1-342) and the associated text identify numerous critical deficiencies in the three reported studies. . When US EPA guidance is applied the study/studies ought to have been screened out from consideration or, at the minimum, be classified as "indeterminate" rather than medium or low confidence. Critical deficiencies included these.

1. The studies of Aslan et al. (2006), Sarsilmaz et al. (2007) and Songur et al. (2003) did not follow any recognized guidelines for assessing developmental neurotoxicity

2. The studies included only two dose levels, whereas developmental neurotoxicity guidelines require three doses (OECD 426).

3. The studies used only "excessive" doses (as cited in the Draft Assessment (i.e., >7 mg/m^3) which resulted in excessive toxicity (i.e., body weight decreases of >10%) at both doses tested. This level of exposure is specifically proscribed in the Guidelines for Neurotoxicity Testing, (US EPA 1998) which states: *"the highest dose level should be the maximum dose which will not induce excessive offspring toxicity, or in utero or neonatal death or malformations, sufficient to preclude a meaningful evaluation of neurotoxicity."*

4. The measures of neurotoxicity (decreased neuronal cell numbers) in the studies have not been validated, which is particularly concerning since more standard pathology observations were not included in the study reports.

5. Incomplete description of methods.

6. The Guidelines for Neurotoxicity Testing, (US EPA 1998) require 20 litters for a valid study, whereas the three studies cited each reported only 3 litters

7. Only two pups/litter were evaluated for each measure, and neither the litter sizes or culling methods were reported

8. The Guidelines for Neurotoxicity Testing, (US EPA 1998) require effects to be based on the litter, but in the cited studies the effects were reported solely on a per pup basis.

These critical and recognized deficiencies in the study/studies support exclusion from evaluation. The Draft Assessment, however, included these reports in their hazard identification (p. 1-359): *"Overall, the evidence suggests, but is not sufficient to infer, that formaldehyde might cause developmental effects on the nervous system, primarily based on studies from the same laboratory"*. The Draft Assessment further used these reports as the basis for requesting additional studies. As noted many times in this peer-review and in the Draft Assessment, there is definitive evidence that inhaled formaldehyde is not distributed systemically. However, in Draft Assessment Table 1-50 (evidence integration) the discussion is concluded with speculation as to results of continued testing: *"Note: confirmatory effects in a medium confidence animal study from another laboratory or in another species, particularly one testing lower exposure levels would be expected to adjust this to evidence indicates [likely]."* This repeated type of speculation, based on "expected" results decreases confidence that the Draft Assessment is based on sound science, but instead speculation supporting a pre-determined outcome.

<u>Example 4: The Draft Assessment often confuses the difference between an adverse and compensatory response, leading to the development of RfCs based on compensatory rather than adverse responses, which is prohibited by EPA guidelines for risk assessment.</u>

Hyperplasia and metaplasia are often compensatory responses, as recognized in the Draft Assessment, but then considered adverse and used for developing RfCs.

As stated in the Draft Assessment, regarding respiratory tract pathology (p. 1-139):

In the URT, both hyperplasia and metaplasia are adaptive tissue responses.

Then, in the same paragraph, it is stated:

> *Along with the acquisition of a protective, barrier-type phenotype, this metaplastic change causes a loss of normal tissue function, including reduced mucous secretion and ciliary clearance. Thus, this loss of normal function is judged to be an adverse outcome in and of itself (i.e., independent from its potential role in progression to cancer). As an interpretation regarding adversity is less clear for hyperplasia, this discussion emphasizes the data on squamous metaplasia.*

First, the data on decreased mucous secretion is not associated with metaplasia observed between 2 and 6 ppm, but rather increased, with documented rhinitis (congestion with runny nose) in animals and humans at these exposure levels. Secondly, metaplasia occurring between 2 and 6 ppm is transitory and increases protection of the nose from irritants, without loss of normal tissue function, but rather with enhanced tissue function. At concentrations $\geqslant$6 ppm, the type of metaplasia changes from a more differentiated and persistent metaplasia; only at these concentrations is normal functioning decreased, and a role in nasal carcinogenesis established (see Thompson et al., 2020 MOA paper in Critical Reviews in Toxicology for a more detailed assessment). Thirdly, it is inconsistent to present a conclusion that the effect is an adaptive response and then to conclude that the same observation is an adverse response.

As stated on p. 1-539:

> *"The evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity"*

However, somewhere in the Draft Assessment, the conclusions regarding the cytotoxicity with regenerative hyperplasia MOA that is at the very least partly operative were lost. Recognition of the importance of this MOA is stated numerous times. For example, in the Overview document (p. 4) it is stated:

> *.. one mechanism contributing to nasal cancer development, specifically cytotoxicity-induced regenerative cell proliferation...*
>
> And, in the Draft Assessment (p. 106)
>
> *Together, genotoxicity, cellular proliferation, and cytotoxicity-induced tissue regenerative proliferation exhibit multiple layers of coherence as a function of species and anatomy, temporality, concentration, and duration of exposure. When integrated, this evidence forms a biologically relevant MOA for formaldehyde-induced URT carcinogenesis (U.S. EPA, 2005a).*

And, in the Draft Assessment (p. 108):

> *Strong and consistent evidence exists which associates the nasal epithelial pathology-driven proliferation with SCC abundance following formaldehyde exposure in rodent experimental models to support a significant role for regenerative proliferation in URT carcinogenesis.*

It is a material error to exclude this information from the data integration and instead only consider mutagenicity as driving the singular MOA. More disturbing is that the mutagenic MOA was then used to justify a decision to derive of a low-dose linear risk (IUR) value for determining cancer inhalation risk, without presenting any alternative for consideration.

Example 5: Epidemiology studies without any analytical sampling should have been excluded from the determination of hazard and/or dose-response.

As stated in the Draft Assessment (Preface p. xxix):

> *"Studies that defined certain occupational groups with considerable exposure to formaldehyde (e.g., embalmers, pathologists, wood or garment workers) as formaldehyde exposed were included, even in the absence of sampling data".*

Below is an example of an epidemiology study, Taskinen et al. (1999), that was graded with medium confidence. This paper should not have been carried forward due to multiple deficiencies, including a lack of analytical data (Table 1-58, p. 1-415):

> *"Human evidence. Moderate for female reproductive or developmental toxicity, based on: Human health effect studies: Two medium confidence studies in two independent populations (decreased fecundability and increased spontaneous abortion risks".*

And,

> *"The evidence indicates that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans."*

Critical Deficiencies in Taskinen et al. (1999), including these.

1. No analytical measurements. Exposures were estimated based on mailed questionnaires.
2. Methanol is a co-exposure that was not accounted for when classifying confidence in this study. This section of the Draft Assessment states (p. 1-366):

   > *"A key consideration for the interpretation of developmental and reproductive outcomes associated with inhalation exposures to formaldehyde in experimental studies was the potential for coexposure to methanol, a known developmental and reproductive toxicant (U.S. EPA, 2013), when the test article was an aqueous solution of formaldehyde. Studies that used formalin but did not control for methanol, and studies that did not characterize the formaldehyde source, are identified throughout this section. Such studies were assigned a low confidence rating.*

   However, despite methanol co-exposures, which were not even listed as potential confounders, the study was graded medium confidence. This was the case for other epidemiological studies with methanol co-exposures that were graded medium confidence in this section of the Draft Assessment.

3. Pregnancy outcomes were evaluated based on recall, in a mailed questionnaire. The period of recall extended over a decade, likely introducing substantial recall bias.

4. Exposures were estimated from an undefined sampling time; when sampling was not available estimates relied upon sampling from an unrelated industry (i.e., cosmetology). This is highly questionable method by which to estimate exposures.
5. The number of women evaluated was not reported for the fecundability ratio; rather this report presented only FDR and 95% confidence limits.
6. The highest risk in the study was calculated for those not wearing gloves (FDR = 0.51) when compared to formaldehyde exposure (FDR = 0.57) or other exposure categories (FDR = 1.09, 0.96 and 0.64 for low, medium and high exposure groups, respectively). The Draft Assessment does not evaluate dermal exposures, based on the lack of systemic distribution, the corrosive nature of formaldehyde (as justified in the Formaldehyde Risk Evaluation Scoping Document), and volatility from skin when not immediately reacted. This fact that not wearing gloves presents the greatest risks calls into question all conclusions related to any cause and effect for formaldehyde in the study.
7. The exposure categories overlapped, raising serious concerns about assignment of individuals to the exposure bands.
    a. Low range 0.01 to 0.3 ppm
    b. Medium range 0.05 to 0.4 ppm
    c. High range 0.15 to 1 ppm.

Given these deficiencies, it was inappropriate to include this study as support for the conclusion that the evidence indicates formaldehyde likely causes an increased risk of human female reproductive toxicity. Rather this study should have been initially screened out from further consideration in the Draft Assessment.

Example 6: Toxicokinetic and Animal Evidence was not Integrated into the Hazard Assessment for Leukemia

In a discussion on decreased strength of evidence, considering mechanistic evidence, (Table IV, p. xl) the Draft Assessment states:

> *"Mechanistic evidence in well-conducted studies that demonstrates that the health effect(s) are unlikely to occur, or only likely to occur under certain scenarios (e.g., above certain exposure levels), can decrease evidence strength."*

And the Draft Assessment (Preface, p. xli, Table V) states:

> *In this assessment, for potential health hazards where the evidence from animal models is likely to influence the overall hazard conclusion, the available mechanistic evidence was considered in light of human relevance.*

There is compelling evidence that inhaled formaldehyde is 1) not systemically distributed at ≤15 ppm, precluding a direct mutagenic MOA; and 2) not leukemogenic in animal models, including transgenic models designed to be sensitive for detecting leukemogenic effects. The Draft Assessment, however, sets aside the evidence that does not support a leukemogenic effect. Rather, the Draft Assessment concludes that formaldehyde is a known human leukemogen, based solely on a non-statistically significant numerical association inconsistently observed in epidemiology studies. This is not reflective of data integration, causal determination based on weight of evidence, or sound science.

8. THE DRAFT ASSESSMENT DOES NOT INCORPORATE ALL LINES OF EVIDENCE INTO THE DOSE RESPONSE ASSESSMENT AND OBSCURES THE OVERLY CONSERVATIVE EFFECTS OF MODELING

As described in the preceding sections, the Draft Assessment did not integrate evidence on exogenous vs. endogenous formaldehyde exposure, nor did it use information on toxicokinetics when modeling the POD/selecting extrapolation methods. Additional examples follow.

Example 1: The Draft Assessment chose to exclude available data but adds uncertainty factors to the POD to account for lack of these same data.

The Draft Assessment (p. 2-28) when justifying an uncertainty factor being applied for extrapolation of subchronic to chronic exposure for respiratory tract pathology states:

> *"A factor of 3 was applied to the respiratory tract pathology POD from Kerns et al. (1983) because it was based on 18-month exposure data from that rodent study in lieu of the 24-month exposure data available in the same study."*

First, it is noteworthy that the 24-month NOAEL for respiratory tract pathology is the same as that defined for the 18-month exposures. Second, the Draft Assessment, in the same paragraph, provides a contradictory analysis by first stating

> *"...there are data to suggest that exposure concentration would be more important to the development of this lesion than duration"*

And

> *"...a lower POD would have been expected if the 24-month data could have been modeled."*

Speculation on what would be "expected," does not present a strong case for adding uncertainty factors for the absence of the excluded data. Thirdly, there are internal inconsistencies in the Draft Assessment when determining to ignore the 24-month data of Kerns et al. (1983). For example, when assessing the results of Ozen et al. (2002), the Draft Assessment (p. 2-24) states:

> *"Although the decreased testis weight data at 4 weeks were successfully modeled[37] (see Appendix B.1.3) to derive a $BMDL_{1SD}$ of 2.60 mg/m^3, this endpoint was not used to calculate a cRfC because a subacute endpoint was not considered an appropriate basis for a chronic RfC when data from longer-term exposure were available from the same study."*

There is no rationale for concluding that a preference for a shorter-term value from the same study is inappropriate in one study evaluation, but acceptable for another study evaluation.

Example 2: The Draft Assessment lacks transparency in the quantitative assessments and conservatism in proposed exposure limits is introduced by the use of modeling practices and exposure concentration adjustments that are ill defined. In addition, insufficient rationale is provided and most often relegated to footnotes. Some resulting uncertainty adjustments exceed the limits defined by EPA.

From the draft IRIS Staff Handbook (EPA, 2021):

The POD for a particular reference value (RfV) is divided by the product of these factors. The RfD/RfC review recommends that any composite factor that exceeds 3,000 represents excessive uncertainty and recommends against relying on the associated RfV.

And,

Uncertainties due to other extrapolations: Toxicity values for which other extrapolations are less uncertain are preferred. For example, a reference value relying on a data-derived adjustment factor for interspecies extrapolation would be less uncertain than a reference value relying on an interspecies extrapolation UF of 10. Note that the size of the composite UF (see Section 13.3) may not be a good indication of the remaining uncertainty because all UFs but the database UF address needed extrapolations (adjustments) or variability, rather than uncertainty (NRC, 2009). Therefore, to avoid "double-counting" or otherwise mischaracterizing uncertainty, the remaining uncertainties that are discussed should be explicitly identified

Example 3: Obscuring the effects of modeling

In Table 2-10 on pages 2-30 and 2-31, NOAELs are not presented and a discussion of the dose levels used in the studies is not provided, in favor of only presenting the POD[a]. The footnotes simply state:

"[a]POD may be adjusted (e.g., to continuous exposure; to a human equivalent concentration."

In the derivation of the cRfC for male reproductive toxicology from Ozen et al. (2002), a POD of 2.91 is listed, with a combined uncertainty factor of 3,000, to yield a cRfC of 0.001 mg/m^3. Without knowledge of the assumptions underlying this calculation, the reader cannot evaluate uncertainty and conservatism in the calculation. The lowest concentration tested in the study was 12 mg/m^3, which is 12,000 times above the calculated osRfC. This highlights that there is more uncertainty in the extrapolation than presented.

Additionally, the Draft Assessment states (p. xxii):

"... higher confidence was placed in the osRfC when the POD was identified close to the range of the observed data."

However, almost all the RfCs and osRfCs were modeled outside of the range of the observed data which introduces substantial uncertainties, none of which appear to be recognized in the draft assessment.

Example 4: The Draft Assessment appears to promote certain conclusions that support a number/specific exposure limits (RfCs and/or Unit Risks) rather than providing rationales for an objective choice.

On p. 3-29 *"An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is within the narrow range (0.006-0.009 mg/m^3) of the group of respiratory system-related RfCs, which together are interpreted with High confidence (sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control"*

EPA guidelines allow a considerable degree of freedom in identifying LOAELs, NOAELs, modeling dose-response, and selecting uncertainty factors. The statement above, however, gives the appearance of conclusions being targeted to a pre-determined number.

Example 5: The Draft Assessment reaffirms the oral RfD developed in 1990 and is currently on IRIS. This exposure limit raises public concern unduly with little likelihood of any recognizable health benefits.

The limited discussion included in the Draft Assessment, and the lack of notice in the IRIS program, it has to be assumed that EPA has no intention of revising the oral RfD for formaldehyde. As quoted on p 2-42 of the Draft Assessment

> *"This RfD was interpreted with medium confidence, based on high confidence in the principal study and medium confidence in the database"*

which is similar to the narrative surrounding the RfCs presented in the Draft Assessment.

A simple ground truthing demonstrates the inappropriate degree of conservatism in the medium confidence RfD. It is well known that formaldehyde is an endogenously produced natural product of metabolism. In addition, there are many studies of the naturally occurring concentrations of formaldehyde in food. For example, in their evaluation of the literature regarding background concentrations of formaldehyde in food, the European Food Safety Authority (EFSA, 2014) calculated the mean concentration of formaldehyde in foods to be 100 mg/kg. Assuming an average human body weight of 70 kg and the oral RfD of 0.2 mg/kg/day, the safe oral dose is 14 mg/person/day. Assuming consumption of 1 kg of food/day/70 kg human, the average human ingests 100 mg formaldehyde/day. As such, our normal diet exceeds the safe exposure level by 7 times the allowable limit. Clearly, this does not reflect actual risk, is not derived from the best available science, is overly conservative, and unnecessarily alarmist.

Example 6: The Ground Truthing for the unit risk for nasal cancer/NPCs provided in the Draft assessment (page 2-53) is fundamentally flawed, because it erroneously and unfoundedly assumes all cases of NPC in humans in the US are related to formaldehyde exposures

EPA describes the ground-truthing of it nasopharyngeal cancer (NPC) slope factor on page 2-53. Specifically:

> *Because NPC is a rare cancer in the United States, with a relatively low number of cases occurring per year, a rough calculation was done to ensure that the unit risk estimate derived for NPC incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population, the IUR estimate for NPC equates to a lifetime extra risk estimate of 4.6 × 10–5. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 180 incident cases of NPC attributable to formaldehyde exposure per year. Alternatively, assuming an average constant lifetime formaldehyde exposure level of 20 ppb, the calculation suggests a crude upper-bound estimate of 730 incident cases of NPC per year. Both upper-bound estimates, using different assumed lifetime exposure levels, are well below the estimated 2,300 total incident NPC cases per year calculated from the SEER NPC incidence rate of 0.75/100,000.*

Although the source of the assumed average constant formaldehyde exposure levels of 5 ppb and 20 ppb in homes were not provided by EPA, it is consistent with the literature. In general, it appears that

the assumption of the average constant lifetime formaldehyde exposure level of 5 ppb and the alternative 20 ppb for the U.S. population was based on Golden (2011).[3]

EPA did not provide calculations to help readers replicate the calculations. However, the crude upper-bound estimate of 180 and 730 incident cases of NPC per year presented in the Draft Assessment appear to be calculated as follows:

- Formaldehyde concentration of 5 ppb x the unit risk of 9.1×10^{-3} per ppm (see EPA's Table 2-19) = a lifetime extra risk estimate of 4.6×10^{-5}.
- The 4.6×10^{-5} lifetime extra risk indicates there will be 4.6 cases of NPC per lifetime in a US population of 100,000.
- In a population of 300,000,000 and for 75 years, the yearly incident cases would be 184 (i.e., $4.6 \times 10^{-5} \times 300{,}000{,}000 \div 75$ years = 184; rounded to 180). Similarly, 20 ppb translates into yearly incident cases of NPC of 728 (rounded to 730).

As noted in the Draft Assessment, the incident cases of 180 to 730 per year at average formaldehyde concentrations of 5 or 20 ppb, respectively, are below the estimated 2,300 total incident NPC cases per year calculated from the SEER NPC incidence rate of 0.75/100,000; (300,000,000 x 0.75) ÷ 100,000 = 2250; rounded to 2300). Another way of looking at EPA's estimates are that they represent either 8 or 32% of the lower bound or mid-point, respectively, of the average concentration in homes to calculate the potential annual cases numbers (i.e., 180 ÷ 2300 or 730 ÷ 2300).

Based on this analysis, the Draft Assessment concluded that its cancer slope factor was reasonable. Is this conclusion justified? We approach an answer to this question through a review of when concentrations of exogenous formaldehyde can cross cell membranes and reach the DNA of nasal epithelial cells, relative dosimetry, a review of NIOSH and SEERs databases, and end with known causes of NPC.

Considering molecular dosimetry data (Leng et al. 2021, Lu et al. 2021) demonstrate that formaldehyde concentrations up to 300 ppb produced no detectable exogenous adducts with a detection limit over 3000 times below the endogenous levels of formaldehyde adducts (i.e., ~2.5 endogenous adducts/10^7 dG adduct versus ≤5 exogenous adducts/10^{11} dG adducts at the detection limit), then the endogenous formaldehyde in the nasal passages would cause >3000 times the incidence that background air concentrations could cause. As such, only <1/3000th of the background rates of nasal tumors in the US could be attributable to inhaled formaldehyde. This means that if all nasal tumors in the US were due to endogenous formaldehyde, which is the maximally conservative assumption, then only a single case of nasal tumors/year could be due to inhaled formaldehyde in a population of over 300,000,000 people, if a mutagenic MOA was operable in this range of exposures.

Additional relevant information on this topic include EPA judgments of other chemicals potentially causing NPC and related tumors. For example, we examined the EPA IRIS database to identify chemicals identified to cause nasal cancers following inhalation exposure. The table below shows that seven IRIS listed chemicals potentially cause nasal cancers, with inhalation unit risks ranging from 1.2×10^{-6} per μg/m^3 (for Epichlorohydrin) to 4.9×10^{-3} per μg/m^3 (for Hydrazine/Hydrazine sulfate). The inhalation unit

[3] Golden, Robert. 2011. Identifying an indoor air exposure limit for formaldehyde considering both irritation and cancer hazards. Crit Rev Toxicol. 2011 Sep; 41(8): 672–721. doi: 10.3109/10408444.2011.573467

risk (IUR) for formaldehyde-induced nasopharyngeal cancer, which includes a mutagenic MOA, is 6.4 × 10^{-6} per µg/m^3, age-adjusted to 1.1 × 10^{-5} per µg/m^3.[4]

Chemicals Listed on EPA IRIS as Causing Nasal Cancers via Inhalation Exposure

Chemical	CASRN	Critical Effect / Tumor Type	Toxicity Value (Inhalation Unit Risk)
Acetaldehyde	75-07-0	Nasal squamous cell carcinoma or adenocarcinoma	2.2 x 10^{-6} per µg/m^3
1,2-Dibromoethane	106-93-4	Nasal cavity (includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, mesotheliomas	6 x 10^{-4} per µg/m^3
1,2-Dibromoethane	106-93-4	Nasal cavity (includes adenoma, adenocarcinoma, papillary adenoma, squamous cell carcinoma, and or/papilloma), hemangiosarcomas, mesotheliomas	3 x 10^{-4} per µg/m^3
1,4-Dioxane	123-91-1	Multiple (nasal, liver, kidney, peritoneal, mammary gland, and Zymbal gland)	5 x 10^{-6} per µg/m^3
Epichlorohydrin	106-89-8	Nasal cavity tumors	1.2 x 10^{-6} per µg/m^3
Formaldehyde		**Nasal pharyngeal tumors**	**6.4 x 10^{-6} per ug/m3**
Hydrazine/Hydrazine sulfate	302-01-2	Nasal cavity adenoma or adenocarcinoma	4.9 x 10^{-3} per µg/m^3
Propylene oxide	75-56-9	Nasal cavity hemangioma or hemangiosarcoma	3.7 x 10^{-6} per µg/m^3

If all nasal tumors were attributed to any one chemical, then the estimated potency of all the other chemicals listed on IRIS would be invalidated. Due to time constraints, we were not able to ground truth each of the above unit risk factors, but this points to the fallacy of assuming all NPCs could possibly be attributed to formaldehyde.

National Institute for Occupational Safety and Health (NIOSH) Analysis

Although smoking risks are not assessed by IRIS, according to NIOSH (1981),[5] cigarette smoke contains as much as 40,000 ppb of formaldehyde by volume, and an individual who smokes a pack of cigarettes a day would inhale ~380 ug. Other researchers also noted that the amount of formaldehyde in

[4] See EPA Table 2-40, page 2-102.
[5] NIOSH (The National Institute for Occupational Safety and Health). 1981. Formaldehyde: Evidence of Carcinogenicity. DHHS (NIOSH) Publication Number 81-111. Available at: https://www.cdc.gov/niosh/docs/81-111/default.html

mainstream smoke of various kinds of cigarettes vary between 3.4 ug to 8.8 ug/cigarette, reported to be equal to concentration between 2,300 to 6,100 ppb (Schaller et al., 1989).[6] The World Health Organization (WHO, 2001)[7] also reported formaldehyde concentrations of 60–130 mg/m^3. For a person smoking 20 cigarettes per day, this would lead to an exposure of ~1,000 ug/day.

Based on these data, it appears that an individual who smokes a pack of cigarette would inhale between 380 and 1,000 ug/day of formaldehyde. Given that EPA assumes that the average daily adult "inhalation rate is 20 m^3/day (EPA, 1989),[8] exposure to 1,000 ug/day of formaldehyde will translate into a concentration of 50 ug/m^3 or 40 ppb. This daily concentration of formaldehyde from cigarette smoke will yield an extra lifetime risk estimate of 3.6×10^{-4} (40 ppb x 9.1×10^{-3} per ppm ÷ 1000 ppb/ppm = 0.00036) or 3.6 cases of NPC in 10,000 smokers per year over and above what EPA has already estimated. For a population of 37,500,000 smokers (0.125[9] x 300,000,000 = 37,500,000) and for 75 years, this extra incident cases in smokers would be 182 per year (3.6×10^{-4} x 37,500,000 ÷ 75 years = 182, rounded to 180).

So, EPA's cancer slope factor is equivalent to either 180 or 730 cases per year, plus the addition of 180 yearly NPC cases in smokers. This translates into either or 360 or 910 cases of NPC or 16 or 40% (i.e., 360 ÷ 2300 or 910 ÷ 2300) of the annual NPC cases in the US due to formaldehyde.

The SEER NPC incidence rate of 0.75/100,000

In the EPA Draft Assessment, Table 1-31 lists the age-adjusted (world) incidence rates of NPC per year in 100,000 people. Out of the 17 references listed, 8 reported data for various locations in the US and almost exclusively, the incidence rate was 0.6/year per 100,000 people. However, EPA did not use this value, but rather calculated their estimated 2,300 total incident NPC cases per year from the SEER NPC incidence rate (of 0.75/100,000). Unfortunately, the software used by EPA is not readily accessible/available to replicate their number.

If the 0.6/100,000 estimates by several researchers that EPA cites are used, the estimated total incident NPC cases per year in the US would be 1800 (i.e., 0.6 x 300,000,000 ÷ 100,000 = 1800). Using this lower annual incidence, which EPA cites, its cancer slope factor is equivalent to either 20 or 51% of the annual NPC cases in the US (i.e., 360 or 910 ÷ 1800 = 20 or 51%).

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[6] Schaller, K. H., Triebig, G., & Beyer, B. 1989. Formaldehyde determination in tobacco smoke--studies under experimental and actual conditions. Zentralblatt fur Hygiene und Umweltmedizin= International Journal of Hygiene and Environmental Medicine, 189(2), 103-110.

[7] WHO (World Health Organization). 2001. Air quality guidelines for Europe, 2nd ed. Chapter 5.8 – Formaldehyde.

[8] USEPA. 1989. Risk Assessment Guidance for Superfund (RAGS) Vol 1: Human Health Evaluation Manual, Part A, Interim Final, Office of Emergency and Remedial Response. EPA/540/1-89-002. U.S. Environmental Protection Agency. Washington D.C. Available at: http://www.epa.gov/oswer/riskassessment/superfund_hh_exposure.htm

[9] See: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

With this view, EPA's cancer slope factor is projecting that either 20 or 51% of the annual NPC in the US is due to formaldehyde exposure alone, depending if the lower end or average mean concentration of formaldehyde in indoor air, respectively, is used in the calculation.

What Are the Causes of NPC identified by other researchers?

We reviewed the literature for the principal causes of NPC. Although several studies have extensively researched this area, a recent publication by Chang et al. (2021) is informative.[10] These authors described the current epidemiologic literature on NPC and highlighted recent results from their population-based case–control study in southern China and other studies. The table below is from Chang et al. (2021) and shows well-confirmed risk factors of NPC and those factors that exert slight to moderate increase in risk or are regarded as possible risk.

[10] Ellen T. Chang, Weimin Ye , Yi-Xin Zeng, and Hans-Olov Adami. 2021. The Evolving Epidemiology of Nasopharyngeal Carcinoma. Cancer Epidemiol Biomarkers Prev 30(6): 1035–1047. doi: 10.1158/1055-9965.EPI-20-1702.

Table From Chang et al. (2021).

Table 2. Risk factors and preventive factors for NPC.

Risk factor	Direction of association[a]
Well-confirmed risk factors	
Older age (up to ~60 years in high-incidence areas)	↑↑
Male sex	↑
Cantonese ethnic background	↑↑
Tobacco smoke	↑
Chinese-style salted fish (in early life)	↑
Epstein–Barr virus infection (positive IgA serology)	↑↑
First-degree family history of NPC	↑↑
Certain *HLA-A* and *HLA-B* alleles	↑/↓
Possible risk factors, based on substantial data	
Indoor air pollution	↑
Other preserved foods	↑
Fresh fruits and vegetables	↓
Epstein–Barr virus sequence variation	↑↑
Chronic respiratory tract infection/inflammation	↑
HIV/AIDS	↑
Occupational wood dust	↑
Other types of occupational dust or smoke	↑
Certain *HLA-D* alleles	↑/↓
Inconsistent findings	
Alcohol	↑/–
Tea	↓/–
Outdoor air pollution	↑/–
Occupational formaldehyde	↑/–
Traditional herbal medicines	↑/↓/–

Abbreviations: HLA, human leukocyte antigen; IgA, immunoglobulin A; NPC, nasopharyngeal carcinoma.
[a]Arrows indicate the approximate magnitude of the relationship, although the magnitude can vary substantially depending on the intensity, duration, and other characteristics of exposure.
↑: slight to moderate increase in risk.
↑↑: moderate to large increase in risk.
↓: slight to moderate decrease in risk.
↓↓: moderate to large decrease in risk.
↑/↓: slight to moderate increase or decrease in risk, depending on genotype or exposure type.
–: no change in risk.

Formaldehyde does not appear to be either a well-confirmed risk factor, nor a possible risk factor based on substantial data by these researchers. Chang et al. (2021) list formaldehyde as an inconsistent finding. This recent report belies EPA's stated cancer slope factor that otherwise projects either 20 or 51% of annual NPC in the US due to formaldehyde.

Nor are the findings of Chang et al. (2021) inconsistent with other agency reports. For example, the WebMD website[11] states that you are more likely to get this type of cancer if you:

- Are male
- Eat a diet rich in salt-cured fish and meats
- Have a family history of nasopharyngeal cancer

[11] See: https://www.webmd.com/cancer/nasopharyngeal-cancer.

- Have certain genes linked to cancer development
- Have come in contact with Epstein-Barr virus

Some, but not all, studies have found a higher risk of NPC in people who:

- Smoke
- Drink a lot of alcohol
- Work around wood dust or a chemical called formaldehyde.

Furthermore, the Cleveland Clinic, the American Cancer Society[12] and Cedars-Sinai[13] state that certain risk factors can increase your chance of developing the disease including:

- Epstein-Barr virus (EBV).
- Salt-cured foods.
- Alcohol and tobacco use.
- Age. Though nasopharyngeal cancer can occur at any age, it's most commonly diagnosed in people between the ages of 30 and 50.
- Race. Nasopharyngeal cancer is more common in people living in Southeast Asia, southern China and northern Africa. People who have immigrated to the United States from Asia also have a higher risk compared to American-born Asians.
- Sex. Men are about two to three times more likely than women to develop nasopharyngeal cancer.
- Family history. If you have a family member with nasopharyngeal cancer, you are more likely to develop the condition.
- Other agents: Exposure to dusts from wood, leather or textiles, as well as inhaling vapors from glue, formaldehyde, solvents, nickel, chromium, rubbing alcohol and radium can increase the risk of nose and sinus cancers, as well as other cancers of the respiratory tract.

Each of these sources indicates that formaldehyde is either a minor contributor to the incidence of NCP in the US or it is absent from any risk factor. So again, is EPA's cancer slope factor reasonable justified? It appears not.

The Bottom Line

EPA's formaldehyde cancer slope factor is not based in reality. It projects that background formaldehyde levels of 5 and 20 ppb will result in 8 and 20% of the annual NPC US incidence in non-smokers, or of 16 and 40% of the population when smokers are included. Moreover, using an EPA cited background NPC incidence of 0.6 per 100,000 folks, EPA's cancer slope factor for formaldehyde, and average indoor formaldehyde concentrations, projects incidences at 20 or 51% of the annual NPC US incidence rate. These values clearly do not match the available literature, which shows minimal, if any, background NPC due to formaldehyde, nor is it consistent with highly reliable biomarker of exposure/molecular dosimetry data that indicates little to any exogenous formaldehyde entering cells at average indoor air concentrations, against a high background of endogenous exposure of the DNA. The

[12] See: https://my.clevelandclinic.org/health/diseases/21661-nasopharyngeal-cancer. And also see: https://www.cancer.org/cancer/nasopharyngeal-cancer/causes-risks-prevention/risk-factors.html.

[13] https://www.cedars-sinai.org/health-library/diseases-and-conditions/n/nasal-and-sinus-tumors.html#:~:text=What%20are%20causes%20and%20risk,cancers%20of%20the%20respiratory%20tract

molecular dosimetry data demonstrates that inhalation exposures could not have added risk of more than 1/3,000th of the endogenous risk. With an average incidence rate of ~2,000 per year in the US, based molecular dosimetry, at maximum formaldehyde could be causing <1 case per year of nasal cancer in a population of 300,000,000 US residents. Clearly, formaldehyde does not present an unreasonable risk of nasal cancer in the US, at average indoor air concentrations.

Example 7: The Draft Assessment does not provide clear rationales for selecting modeling approaches.

The Draft Assessment does not present explicit rationales for selecting a particular benchmark dose (BMD) or for choosing BMD over a LOAEL/NOAEL approach. In particular it must be clarified when effects are observed at concentrations above the range of saturable metabolism (i.e., 1-2 ppm for formaldehyde), but extrapolated to doses below the range of saturable metabolism.

The EPA (2021) draft IRIS Staff Handbook highlights the error of extrapolating from high dose study results at concentrations above those which saturate normal removal processes to concentrations below which normal metabolism is saturated, when stating:

> *"...if only excessively high exposure levels were tested, is there reason (e.g., an experimentally validated, substantial difference in toxicokinetics at different exposure levels; observed or inferable nonspecific toxicity) to believe that the observed responses might be dissimilar to responses that might occur at lower exposure levels?"*

And,

> *"Basis of the POD: A modeled BMDL is preferred over a NOAEL, which is in turn preferred over a LOAEL. Additionally, when there is sufficient knowledge of toxicokinetics and the active toxic agent for the effect, a POD based on an internal dose metric would be preferred over one based on administered exposure"*

For example, P 2-76: When discussing cell division rates predicted in the BBDR model, the Draft Assessment states:

> *There are currently no data of any kind, even in rats, to inform the effect of formaldehyde on the kinetics of initiated cells. However, assuming that the initiated cells related to tumors in the respiratory tract can be identified and their division rates measured, it is reasonable to suppose that these rates would be at least as variable as division rates of normal cells. Based on the normal variation in such rates observed in normal cells in Figure 2-7, and the extreme sensitivity of the formaldehyde model to small differences in assumed division rates of initiated cells, EPA concluded that it would be impossible to measure these accurately enough to lead to any substantive reduction in the large uncertainty in the risk estimated by this model.*

On p. 2-77, EPA uses modeling of cell division rates and related hyperplasia, from concentrations within and above the range of metabolic saturation (i.e., 1-2 ppm), to estimate the POD for cell division at lower concentrations, rather than using the NOAEL identified in animal studies, and states:

> *Therefore, the rat BBDR models are used to calculate benchmark concentrations for these PODs, and the benchmark response was extended slightly below the observed.*

The conclusion reached in the Draft Assessment (p. 2-78) is:

The following benchmark PODs and corresponding HECs were developed based on increased cell proliferation as well as hyperplasia: (a) 0.44 ppm (0.54 mg/m3) corresponding to the BMCL01 in Schlosser et al. (2003), and roughly two- to three-fold lower estimates based on examining data from other cell labeling studies (as discussed above in the section on modeling precursor lesion data), resulting in an overall range from 0.18 to 0.54 mg/m3; and (b) 0.16 ppm (0.20 mg/m3) based on EPA's modeling of the incidence of basal hyperplasia reported by Kleinnijenhuis et al. (2013) in Wistar rats. To these values, it is necessary to apply a UF = 3 to reflect other uncertainties in extrapolating from animals to humans and a UF = 10 to account for human variability (total UF = 30). This results in cRfCs that range from ***0.006 mg/m³ to 0.018 mg/m³*** *when based on cell proliferation data and a cRfC of* ***0.007 mg/m³*** *from the hyperplasia data.*

Example 8: The Draft Assessment concludes that a mutagenic MOA is operative for nasal tumors and, therefore, low dose linear extrapolation is required and fails to integrate data demonstrating that both the tumorigenic response and exposure to the molecular target (i.e., DNA) are highly non-linear.

As stated in USEPA (2005) Cancer Risk Assessment Guidelines:

> *Toxicokinetic studies may contribute to mode of action analysis by contributing to identifying the active form(s) of an agent that is central to the mode of action. Apart from contributing in this way, toxicokinetics studies may reveal effects of saturation of metabolic processes. These may not be considered key events in a mode of action, but they are given separate consideration in assessing dose metrics and potential nonlinearity of the dose-response relationship.*

[Note: This is almost identical to the approach taken by Thompson et al. (2020) and identified as Key Events 1 and 2 in the MOA, a manuscript that was notably excluded from evaluation.]

And

> *Toxicokinetic models can improve dose-response assessment by revealing and describing nonlinear relationships between applied and internal dose. Nonlinearity observed in a dose response curve often can be attributed to toxicokinetics (Hoel et al., 1983; Gaylor et al., 1994), involving, for example, saturation or induction of enzymatic processes at high doses.*

On page 2-82, Table 2-28, the Draft Assessment lists the *"Strengths and uncertainties in the cancer type-specific unit risk estimate for nasopharyngeal cancer."* The strength of the evidence is listed as being medium, and that the unit risk estimate as reliable, based on the strengths and uncertainties listed. However, saying a strength is that *"linear low-dose extrapolation is supported by a mutagenic mode of action"* is not warranted because the exposure to the DNA is highly non-linear (Leng et al. 2019). Furthermore, the tumor response modeled was not statistically significant, even at the highest cumulative exposure assessed in the epidemiological literature; this is recognized in the Draft Assessment as an "uncertainty". Note also the tumors observed in animals have a highly non-linear dose response: <1% at 6 ppm and >40% at 15 ppm.

The Draft Assessment Table 2-28 lists an uncertainty in the low-dose extrapolation as *"based on the potential for endogenous formaldehyde to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling"*. This is an unfounded assertion as modeling does not demonstrate anything

but is more appropriately characterized as a hypothesis generating tool. Numerous molecular dosimetry experiments do, in fact, demonstrate that the highly non-linear exposure of tissues to inhaled formaldehyde is unrelated to endogenous formaldehyde, but rather is due to independent factors (e.g., saturation of metabolism and other removal mechanisms).

That the Draft Assessment does not identify some critical uncertainties is of great concern. They include these.

1) The cancer response in humans that was modeled as linear at low dose. This response was statistically significant only at the highest concentration evaluated, and thus it is highly non-linear.

2) The tumor response in animals was also highly non-linear, with no tumors observed at concentrations that did not saturate metabolism and removal processes (i.e., <4 ppm).

3) The Draft Assessment dose response assessment did not address the substantial literature demonstrating molecular dosimetry at the putative molecular target is highly non-linear (DNA adduct formation).

4) The Draft Assessment dose response assessment did not incorporate the peer-reviewed literature supporting a non-mutagenic non-linear MOA, based on cytotoxicity with regenerative cell proliferation.

5) The Draft Assessment dose response assessment did not consider other human studies that did not show an association of NPCs and inhaled formaldehyde.

We also have concerns with items listed as strengths in the Draft Assessment including.

1) *"detailed, individual cumulative exposure estimates"* This does not acknowledge that using estimated parameters contributes to the overall uncertainty regarding the validity of conclusions.

2) *"Low-dose linear extrapolation is supported by a mutagenic mode of action (i.e., not a default)"*. The assumption of low dose linearity for high dose formaldehyde effects is not appropriate. There is no evidence of in vivo mutagenicity below the concentration range where the metabolic saturation limit for inhaled formaldehyde is observed (i.e., 0.7 to 2 ppm). Instead, there are molecular dosimetry data that argue against a mutagenic mode of action, even at concentrations at which the tumors were observed

3) *"Similar unit risk estimates derived using rat bioassay and mechanistic data on nasal cancers"* is not a strength. The alignment of two default approaches, each with numerous uncertainties, does not support a single medium reliability determination.

It is also concerning that the Draft Assessment claims that linear extrapolation is supported by EPA's Cancer Risk Assessment Guidelines in the absence of a convincing formal (i.e. framework-driven) demonstration of a mutagenic MOA. , Furthermore, the Draft Assessment (p. 2-79) states toxicokinetic considerations have been considered in extrapolation.

Following the procedures in EPA's cancer guidelines (U.S. EPA, 2005a) to be applied when knowledge of the MOA does not support an alternative approach or when direct mutagenicity

does not contribute to the cancer response, this extrapolation was carried out as a straight line drawn to the origin from the HEC corresponding to the BMDL.

Despite the above claim, we note that no real consideration was given to toxicokinetics. The toxicokinetics/molecular dosimetry data demonstrate that DNA in the nasal epithelium is not exposed to formaldehyde at concentrations ≤0.3 ppm and does not support linear extrapolation.

Example 9: Since formaldehyde is an irritant gas, where concentration is of greater importance than time of exposure, time adjustments were inappropriately applied when deriving RfCs.

As stated in EPA guidelines (Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, 1994):

"The rationale for this linear prorate adjustment is that the resultant human exposure concentration should be the concentration (C) × time (T) equivalent of the experimental animal exposure level. This adjustment is weakly founded because steady-state conditions may not be reached in laboratory animals for some chemicals and intermittent regimens and because the influence of dose-rate is different for different toxicity mechanisms (e.g., an effect mediated by peak blood concentration versus integrated tissue dose). Thus, depending on the mechanism of action, such duration adjustment may be inappropriate. Toxic effects of gases such as irritation, narcosis or asphyxia may be much more dependent on concentration than duration. An attempt should always be made to take into account the mechanisms of toxic action as related to the temporal parameters of duration and frequency."

A specific example of this is taken from the Draft Assessment review of the Ozen et al. (2002) study. The LOAEL of 12.2 mg/m^3 was "adjusted" to 2.91 mg/m^3, based on intermittent exposure in the rat study (6 hr/day, 5 days/wk) to continuous exposure for humans.

Example 10: Toxicodynamics and toxicokinetics considerations, demonstrating highly non-linear dosimetry, were not taken into consideration when deriving quantitative estimates of risk.

In the preface to the Draft Assessment (p. xix), it is stated:

"The evaluation of formaldehyde's toxicity was informed by what is known about the toxicokinetics of inhaled formaldehyde (see Section 1.1.3 and Appendix A-2), and this knowledge is reflected in organization of the Hazard Identification section."

Also, in the Draft Assessment preface (p. xxi) it is stated:

Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the upper respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde.

These two statements are directly contradictory. The evaluation is not informed by toxicokinetics or toxicodynamics of formaldehyde. These are dismissed from consideration, with the assumption that formaldehyde acts via an unknown pathway to elicit systemic effects at highly toxic concentrations (i.e., ≥6 ppm). In direct conflict with scientific evidence that inhaled formaldehyde is not systemically distributed at inhalation concentrations of ≤15 ppm.

Example 11: The Draft Assessment does not integrate available data, as required when reaching conclusions; individualRfC and Inhalation Unit Risk (IUR) factors were calculated based on individual study results with only uncertainty factors added and/or linear extrapolations. The exception is an inappropriately averaged RfC for female reproductive or developmental toxicity.

As stated in the EPA guidelines A Review of the Reference Dose and Reference Concentration Process, (US EPA 2002):

> *Risk Characterization: The integration of information on hazard, exposure, and dose response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.*

Another EPA guideline, Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, (US EPA 1994) says this:

> *With each progressive level [of integration], incorporation and integration of mechanistic determinants allow elucidation of the exposure-dose-response continuum and thus, a more accurate characterization of the pathogenesis process.*

And,

> *However, whenever the data base permits, the most robust qualitative evaluation typically involves an integrated interpretation of human and animal data, taking advantage of the unique strengths of each.*

And,

> *Therefore, although the deposition, clearance mechanisms, and physiochemical properties of the agent are described in distinct sections, assessment of the overall toxicity requires integration of the various factors.*

And,

> *The relative contribution or interaction of these is, in turn, affected by the exposure conditions (concentration and duration), so that as emphasized previously, integration of these various factors is necessary to estimate the deposited (on airway surfaces) and absorbed doses in order to assess toxicity.*

The Draft Assessment Table ES-1 (p. lii): "Evidence integration/judgments for noncancer health effects and the reference concentration (RfC)" presents seven RfCs, each developed for a different endpoint. Except for the RfC for asthma and the RfC for respiratory tract pathology, the other osRfCs were derived from single studies and useing a combination of modeling and uncertainty factors. Although it could be considered justified to combine the PODs from multiple studies assessing asthma, it is not standard practice nor is it transparent in the absence of a supporting rationale.

By contrast, the osRfC for respiratory tract pathology, was based on two different studies with different endpoints. This approach is not supported by EPA guidance. It is never appropriate to combine results from two completely disparate endpoints (i.e., asthma in a human study and metaplasia in a rat study) to calculate a singular POD and then to adjust that hybrid POD by application of uncertainty factors.

The other five RfCs in Table ES-1 are each based on single study that was modeled to develop a POD. The Assessment did not provide a sufficient rationale for the choice of the not identifying POD. After applying uncertainty factors, the resulting RfCs were all "integrated" to support a singular RfC of 0.007 mg/m^3. The basis for the RfC is stated to be (Table ES-1, footnote a):

> *Basis for RfC—sensory irritation, decreased pulmonary function, current asthma symptoms or degree of asthma control, and allergic conditions. The corresponding osRfCs (i.e., based on human studies with medium or high confidence in the health effects and PODs) are highlighted in gray, which also have the lowest UFC values.*

Combining different RfCs into a singular RfC is not supported by EPA guidance. Providing the rationale for a choice of quantitative estimate is not integration of evidence. A rationale could be a policy-based, conservative approach of choosing the lowest quantitative estimate, but is not a scientifically justified approach. Another justifiable rationale for choice would be the estimate for which there is strongest scientific support of human relevance. The current method in the Draft Assessment of combining different RfCs into a singular RfC must be eliminated to be consistent with USEPA guidance and standard risk assessment practice.

Example 12: The Draft Assessment does not integrate the evidence developing IURs for nasal cancer and leukemia andfails to integrate of animal studies, toxicodynamics, toxicokinetics, or dosimetry into the modeling.

The same EPA guidance quotes, provided above in Example 3, are relevant to data integration for hazard assessment and dose response for nasal tumors and leukemia.

Dismissing and/or misrepresenting genotoxicity studies, animal data, Biological Based Dose Response (BBDR) modeling, toxicokinetics, toxicodynamics, prior conclusions by other regulatory bodies and the peer-reviewed literature on MOAs is not integrating the evidence. The statements made in the Draft Assessment do not reflect the totality of the data. However, the Draft Assessment quotes below reflect a general dismissal of important points, and apply default-based methods, that do not reflect a formal evaluation of data.

As stated in the Draft Assessment (Executive Summary, p. lv, Table ES-2):

> *The judgment of evidence demonstrates for NPC cancer is based on robust human evidence of increased risk in groups exposed to occupational formaldehyde levels, and robust animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity, epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion.*
>
> *While the preferred unit risk estimate for NPC is based on a cancer mortality study in humans, several estimates in general agreement with each other were also derived based on animal nasal tumor incidence. These estimates used multiple mechanistic and statistical models, including biologically based dose-response (BBDR) modeling (see Section 2.2.2). In addition, an RfC for one mechanism contributing to nasal cancer development, specifically cytotoxicity-induced*

regenerative cell proliferation, was estimated to be between 0.006 and 0.018 mg/m^3 based on calculations using animal data. Specifically, this narrow RfC range was estimated based on cRfCs from a pathology study of hyperplasia, labeling studies of proliferating cells, and BBDR modeling results (see Section 2.2.2).

NA = not applicable; an ADAF-adjusted value was not calculated for the unit risk estimates based on the animal data on nasal cancer, as the human unit risk estimate for NPC was the preferred estimate.

Why was this estimate not done for comparison with the unit risk from human studies, where there are highly non-linear processes for each endpoint for nasal tumors?

Similarly, the Draft Assessment states for leukemia:

The judgment of evidence demonstrates for myeloid leukemia is based on robust human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations. The animal evidence is inadequate and the findings to date suggest that there may be a lack of concordance across species for leukemia, as leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for LHP cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the upper respiratory tract to distal tissues).

fNA = not applicable; no ADAF adjustment is recommended for myeloid leukemia because the MOA is unknown (see Section 1.3.3).

gThe full lifetime (ADAF-adjusted) IUR estimate is based on the ADAF-adjusted estimate for nasopharyngeal cancer (which includes a mutagenic MOA; see Section 1.2.5). Less-than-lifetime exposure scenarios with a very large fraction of exposure during adulthood may not warrant ADAF adjustment, and one may choose to use the unadjusted unit risk estimate of 6.4 × 10^{-6} per μg/m^3. Otherwise, see Table 2-39 for an illustration of how to apply the ADAFs to obtain total cancer risk estimates for less-than-lifetime exposure scenarios (see Section 2.2.4).

Example 13: The Draft Assessment frequently combines "statistics not reported" with "not statistically significant" and undefined "significant" determinations. The basis for statistical and biological relevance as treatment-related is not transparent.

Table 1-22 is five pages long and includes dozens of studies, is overly complex, and includes almost a full page of footnotes. The table is not clear or transparent in presentation. Furthermore, the reliability of the assessment is obfuscated by combining statistical significance and reported and undefined "significance" in the same category.

Footnote "a" (p. 1-316) states:

"Primarily, this reflects reporting of a statistically significant change; in rare instances where a p-value was not given, changes are indicated if the authors discussed the change as a significant effect."

This approach obscures what is a statistically significant effect and what is considered a "significant" effect; confusing rather than informing the reader. The unjustified binning of scientifically based methods (i.e., statistics) with undefined judgments should not be carried forward to further drafts.

Similarly, Table 1-39 column 3 is titled "Statistical associations". The footnote shows that NR means either that no statistics were done or that no significant association was reported.

Footnote d (page 1-239) states:

"Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+), weakly positive (–/+) associations, inverse association (–); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]), apical portal of entry (POE)."

The same footnote is also included in Table 1-41 (p. 1-298)

Similar to the example immediately above, this approach obscures what is a statistically significant effect and what is considered a "significant" effect and confuses rather than informs the reviewer. This unjustified binning of scientifically based methods (i.e., statistics) with undefined judgments must not be carried forward to further drafts.

See comments on studies including Aslan et al. (2006), Sarsilmaz et al. (2007), Songur et al. (2003), Ozen et al., (2005).

Example 14: Inappropriately the Draft Assessment does not justify the large quantitative differences in EPA's hazard and dose-response assessments when compared to recently published exposure guidelines and limits by both WHO and the European Commission, respectively.

Each of these authoritative bodies derived safe exposure levels up to three orders of magnitude higher than the safe exposure limits (RfCs and IURs) presented in the Draft Assessment.

The Draft Assessment does not compare the derived safe exposure levels (i.e., RfCs and IURs indicating a value within the 10-4 – 10-6 acceptable risk range) to international standards, such as the recently published updated WHO Indoor Air Quality Guideline or the European Union occupational exposure limit. A comparison of the acceptable exposure limits (e.g., RfCs and DNELs) follows.

	Air, General Population (mg/m^3)	Air, Workplace (mg/m^3)
Draft IRIS Assessment RfC	0.007 composite 0.001 for reproductive effects	Not derived
Draft IRIS Assessment	0.00011 (at 10^{-6} de minimis risk)	
WHO Indoor Air Quality Guideline	0.1	Not derived
EU SCOEL	Not Derived	0.369

Such a comparison is required by TSCA as detailed in: Attachment—Additional Questions for the Record Subcommittee on Environment and Climate Change Hearing on "TSCA and Public Health: Fulfilling the Promise of the Lautenberg Act" October 27, 2021. The Honorable Michal Ilana Freedhoff, Ph.D., Assistant Administrator, Office of Chemical Safety and Pollution Prevention (OCSPP), U.S. Environmental Protection Agency and cited, as follows.

> *"Question: Is it reasonable to expect a scientist to justify his or her view based on citations to the literature to existing EPA policies and guidance, and/or international standards (such as Organization for Economic Cooperation and Development (OECD) guidance)?*
>
> *Response: Yes; in fact, EPA risk assessment guidance requires assessors to do so. For example, EPA's Risk Characterization Policy Handbook (in effect since 2001) requires risk characterizations to be transparent and the risk characterization products clear, consistent, and reasonable (TCCR). It states: "The risk characterization criteria of TCCR are essential, because new rules, and the work products supporting them, must often withstand intense scrutiny by the general public and the stakeholders affected by EPA's decisions."*

The Draft Assessment often omits any discussion of the hazard conclusions reached by the WHO and ECHA. The conclusions from these authoritative bodies do not support those in the Draft Assessments, and an explanation of why is required in any future drafts of the IRIS Formaldehyde Assessment.

9. THE DRAFT ASSESSMENT DOES NOT INTEGRATE INFORMATION ON MOA INTO THE HAZARD IDENTIFICATION OR DOSE RESPONSE AS REQUIRED BY EPA GUIDELINES

A major deficiency in the Draft Assessment is the lack of a demonstrated MOA using the US EPA framework in the Guidelines for Cancer Risk Assessment (2005) or an alternative such as the WHO International Programme on Chemical Safety (IPCS) framework for human relevance. This deficiency and some other difficulties with MOA use in the Draft Assessment are described in some examples below:

<u>Example 1: The Draft Assessment does not follow the EPA Framework in presenting alternative MOAs and including the empirical support for each.</u>

NAS (2009) Science and Judgement in Risk Assessment emphasizes the importance on presenting alternative MOAs, when stating:

> *If information on the mechanism of cancer induction suggests that the slope of the linearized multistage model is not appropriate for extrapolation, this information should be made an explicit part of the risk assessment. If sufficient information is available for an alternative extrapolation, a quantitative estimate should be made. EPA should develop criteria for determining what constitutes sufficient information to support an alternative extrapolation. The evidence for both estimates should be made available to the risk manager.*

This is directly relevant to the discussion of the cytotoxicity and regenerative hyperplasia MOA for nasal tumors related to inhaled formaldehyde. The Draft Assessment does not reference the Thompson et al. (2020) IPCS MOA analysis for formaldehyde-related nasal tumors that updated the McGregor et al.

(2006) assessment. This despite written and oral communications to the EPA from the authors and sponsors. Rather the Draft Assessment acknowledges the MOA as defined by McGregor et al. (2006), as updated by Thompson et al., but without referencing those peer-reviewed publications (see quote below). Furthermore, the Draft Assessment dismisses the MOA, in favor of a mutagenic MOA, without making a quantitative assessment of the cytotoxicity with regenerative hyperplasia MOA as directed by the NAS (2011). The Draft Assessment first states (p. 1-186):

> *Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when these factors are integrated, they form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis.*

And, then states on the next page (p. 187):

> *The evidence is sufficient to conclude that a mutagenic mode of action of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.*

At the minimum, any revisions of the Draft Assessment must provide quantitative estimates for both the peer-reviewed cytotoxicity with regenerative hyperplasia MOA for nasal tumors, as well as a default mutagenic MOA (with linear low-dose extrapolation). Note that neither the US EPA Cancer Guidelines nor the IPCS MOA Framework describe a "default" MOA. Any hypothesized MOA is to be evaluated using modified Bradford-Hill criteria applied to empirical observations and address dose-response.

Lastly, in contrast to presenting an dispassionate evaluation of the peer-reviewed cytotoxicity and regenerative hyperplasia MOA for nasal tumors, the Draft Assessment presents "An integrated cancer mode-of-action (MOA) network for the URT" based on key characteristics of carcinogens. This is followed by lengthy speculation on how the network may result in tumors. As noted previously in these comments, there is no structured evaluation of the cytotoxicity and regenerative hyperplasia MOA as recommended by IPCS guidelines and required by the US EPA Guidelines for Cancer Risk Assessment. Examples of the speculative nature of the MOA and of the discussion of the "integrated cancer mode-of-action (MOA) network for the URT" is highlighted in the quotations below (p. 1-292.

> *Evidence from humans and rodents suggests that formaldehyde exposure can lead to increasing levels of reactive oxidative species (ROS) and possibly inhibit cellular detoxification mechanisms (see Appendix A.5.6), which would be expected to further exacerbate oxidative damage to cellular constituents and DPX formation. Following these initial effects, single-strand DNA breaks could be created more frequently, and DNA repair could be inhibited, possibly leading to an accumulation of genetic damage at the chromosome (clastogenicity) and sequence level (gene mutations). [Emphasis added]*

This discussion leads to an assumption-based rather than evidence-based assessment. Such assumption-based discussions must be greatly reduced or eliminated in any further iterations of the Draft Assessment.

Example 2; the Draft Assessment does not include a fair evaluation of the most widely accepted MOA for nasal tumor formation related to formaldehyde and does not follow EPA Cancer Guidelines

[See also general comments on lack of documentation for MOA].

Over the past 30 years, the MOA of cytotoxicity with regenerative hyperplasia for nasal tumors/NPC has become globally accepted. A former director of the IRIS program is one of four authors on the first peer-reviewed publication detailing the cytotoxic with regenerative hyperplasia MOA for nasal tumors (McGreggor et al. 2006), which was recently updated and published by Thompson et al. (2020). McGreggor et al. (2006) was cited in one paragraph of the Draft Assessment as evidence against the cytotoxicity MOA. The exclusion of Thompson et al. (2020) from the Draft Assessment is noteworthy, as Dr. Thompson personally briefed the EPA IRIS staff on the peer-reviewed and published cytotoxicity MOA. This MOA for nasal tumors was recently adopted by the European Chemicals Agency (ECHA) and approved by the 32 countries in the European Union. While the Draft Assessment says that nasal tumors/NPC have a mutagenic MOA, there is neither a formal determination as described in the Guidelines for Cancer Risk Assessment (US EPA 2005) nor is there an assessment of the data-driven, framework organized, alternative of cytotoxicity with regenerative hyperplasia, as described and required by the EPA (2005) Cancer Risk Assessment Guidelines.

EPA Cancer Risk Assessment Guidelines (2005) state:

> *"If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager. In this case, the default model not only fits the data, but also serves as a benchmark for comparison with other analyses. This case also highlights the importance of extensive experimentation to support a conclusion about mode of action, including addressing the issue of whether alternative modes of action are also plausible."*

And

> *"Rather, these important considerations are taken into account throughout the assessment with a goal of producing an objective appraisal of the evidence (informed by peer and public comment and advice), which includes the weighing of alternative views on controversial issues."*

And

> *"Toxicokinetic models can improve dose-response assessment by revealing and describing nonlinear relationships between applied and internal dose. Nonlinearity observed in a dose response curve often can be attributed to toxicokinetics (Hoel et al., 1983; Gaylor et al., 1994), involving, for example, saturation or induction of enzymatic processes at high doses."*

And,

> *"For cases where the tumors arise through a nonlinear mode of action, an oral reference dose or an inhalation reference concentration, or both, should be developed in accordance with EPA's established practice for developing such values, taking into consideration the factors summarized in the characterization of the POD (see Section 3.2.5). This approach expands the past focus of such reference values (previously reserved for effects other than cancer) to include carcinogenic effects determined to have a nonlinear mode of action."*

Despite saying EPA determined a mutagenic MOA to be operable, no evidence of any dose-response for mutagenicity was presented and no concordance with tumor incidence was provided. In any future drafts of the Draft Assessment, if a mutagenic MOA for NPC is still supported, toxicokinetics and time and dose-concordance must be addressed and the data integrated into the dose response assessment, as required by EPA guidance.

Example 3: Mechanistic evidence demonstrating inhaled formaldehyde is not distributed beyond the upper respiratory tract is dismissed, and not integrated into the assessment, for numerous endpoints, such as leukemia

As stated in the EPA (2005) Cancer Risk Assessment Guidelines:

Toxicokinetic studies may contribute to mode of action analysis by contributing to identifying the active form(s) of an agent that is central to the mode of action. Apart from contributing in this way, toxicokinetics studies may reveal effects of saturation of metabolic processes. These may not be considered key events in a mode of action, but they are given separate consideration in assessing dose metrics and potential nonlinearity of the dose-response relationship.

And, as stated in the draft IRIS Staff Handbook (2021):

> *"Are there notable uncertainties in the sets of human or animal health effect studies for which related mechanistic information is available? An understanding of mechanistic pathways (e.g., by identifying mechanistic precursor events linked qualitatively or quantitatively to apical health effect[s]) can influence the strength of the evidence integration conclusions, providing either support for or against biological plausibility."*

And,

> *"Relating adverse response to an appropriate internal tissue dose rather than administered dose or concentration is likely to improve the characterization of dose-response relationships (U.S. EPA, 2006a)."*

It is clear that toxicokinetic considerations are key to integrating the multiple streams of evidence necessary to make a sound data-driven conclusion. However, for leukemia, the Draft Assessment disregarded the wealth of information available that demonstrates that inhaled formaldehyde is not systemically distributed as well as dosimetry related to the naturally occurring background tissue concentrations of formaldehyde. Instead, the Draft Assessment relied on pure speculation to support what was apparently a pre-determined outcome. Notably, there is not one place in the Draft Assessment where the evidence against there being a mechanism of LHP carcinogenesis following inhalation exposure to formaldehyde is objectively discussed.

In the discussion of leukemia, the Draft Assessment sets aside the wealth of information available on the lack of systemic distribution of inhaled formaldehyde, as well as dosimetry related to the naturally occurring background tissue concentrations of formaldehyde. The Draft rather provides a lengthy mechanistic speculation to explain the possibility of an association of exogenous formaldehyde exposure and leukemias.

There is no section in the Draft Assessment that formally evaluates evidence for a MOA of LHP carcinogenesis following inhalation exposure to formaldehyde. However, the Draft Assessment devotes a significant effort in an attempt to support their conclusion as summarized in the below excerpts from the document.

Page 1-496, begins with a conclusory statement:

> *This section evaluates evidence supporting plausible mechanisms of LHP carcinogenesis following inhalation exposure to formaldehyde.*

Three pages later, there is some effort to provide a coherent rationale linking formaldehyde to LHP, by stating (p. 1-498)

> *The approach taken in this section was to identify mechanistic events possibly linking inhaled formaldehyde-induced effects to LHP cancer risk in humans, and then to evaluate the supporting evidence for these events and relationships.*

While on p. 1-503, recognizing the lack of mechanistic evidence to support the leukemogenic hypothesis by the statement:

> *Although no evidence exists to evaluate the following potential scenarios, there are at least three ways in which formaldehyde exposure (with distribution limited to the URT) might cause these genotoxic effects: (1) direct interaction of formaldehyde with HSPCs in the URT; (2) indirect effects on circulating or bone marrow HSPCs due to secondary, systemic effects following formaldehyde-induced changes in the URT; and (3) modification and mobilization of precursor-type cells residing in the URT. (Emphasis added).*

And concluding {correctly} on p. 1-504:

> *Overall, the evidence largely does not exist to determine whether any of the proposed processes explain how formaldehyde exposure might cause genotoxicity in HSPCs. [Emphasis added]*
> After four more pages of speculation about how genotoxic responses in the absence of exposure could occur, the Draft Assessment (p. 1- 508) states:
>
> *Looking across studies, the overall pattern of these responses across exposure levels and exposure durations is difficult to interpret.*

Op. 1-510 the Draft Assessment states:

> *Overall, while several studies indicate effects on hematopoietic cell populations and secreted factors, for which exposure concentration may be an important determinant, the impact of these changes on leukemogenesis cannot be clearly discerned.*

And on p. 1-511 on the subject of DNA damage, the Draft Assessment proceeds to state:

> *Overall, together with the genotoxicity data, this evidence indicates the likely presence of DNA damage and, possibly coincidentally, the likely presence of elevated oxidative stress in circulating leukocytes, although the data are insufficient to describe this potential relationship in terms of duration or concentration of exposure.*

And on p. 1-512 regarding oxidative stress, the Draft Assessment, states:

> *In summary, the potential relationship of increased systemic oxidative stress to LHP carcinogenesis is unknown.*

Furthermore, regarding bone marrow impacts, the Draft Assessment (p. 1-512, the Draft Assessment states:

> *In general, the data relevant to potential formaldehyde-induced changes in the bone marrow niche were fairly weak and inconsistent across the available studies*

Further regarding bone marrow impacts, the Draft Assessment (p. 1-514), the Draft Assessment states:

> *Based on the currently available data, no conclusions can be drawn regarding he potential involvement of formaldehyde exposure-induced indirect effects on the bone marrow niche in LHP carcinogenesis.*

The Draft Assessment purportedly integrates these weak and inconsistent data to stating on p. 1-515:

> *"Following formaldehyde exposure, the available evidence supports the following observations: (a) elevated levels or severity of DNA or chromosomal damage in circulating human blood cells, including in both myeloblasts and mature lymphocyte populations; (b) the specific nature of DNA damage in circulating human leukocytes exhibits aneugenic characteristics similar to damage reported in humans with or at increased risk for AML; and (c) that the human immune system is impacted, possibly as a function of formaldehyde concentration, in a complex manner."*

And,

> *"Despite the internal consistency of many of the individual effects described above regarding formaldehyde-induced damage to target cells and biomarkers of genotoxicity in circulating mature PBLs in humans, <u>there is a general lack of understanding regarding both how formaldehyde exposure might cause these changes, as well as how these mechanistic events may lead to LHP cancer.</u> [Emphasis added]"*

The Draft Assessment (p. 1-517) further states:

> *"The mechanisms responsible for these observations are unclear, as is any specific contribution of these mechanistic events to LHP carcinogenesis. Likewise, although some evidence exists to support increased systemic oxidative stress associated with formaldehyde exposure, its role in targets of LHP cancers is also unclear, and any specific impacts on immune function or tumor immunosurveillance remain to be determined."*

The speculation, in the absence of any compelling and consistent data continues, on p. 517 where it is stated:

> *"A hypothesized scenario that does not require bone marrow cytotoxicity is that HSPCs damaged in the URT tissues do not return to the bone marrow but form local neoplastic foci. <u>However, there is no evidence supporting this possibility."</u> [Emphasis added]*

The lengthy and speculative evidence integration in the Draft Assessment concludes on p. 1-519:

"While the available mechanistic database has limitations, this does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia in epidemiology studies."

It is difficult to maintain that the non-statistically significant association represents causality for formaldehyde and leukemias, in the absence of any plausible, empirically demonstrated means whereby this could occur, in the absence of any identified risks for leukemia in reliable cancer bioassays or in the absence of systemic distribution.

For leukemia, NTP (2011) likewise did not integrate evidence in their hazard classification for formaldehyde carcinogenic potential, when concluding formaldehyde is a Known Human Carcinogen for Leukemia. However, neither IARC and NTP considered potential mechanistic information, as their guidelines do not require an integration of the data. Furthermore, neither conducted their analyses according to a recognized framework. According to their guidelines, these bodies defaulted to an epidemiology-only assessment of hazard. In contrast, and with better science, evidence integration, which included an analysis of evidence against formaldehyde being a leukemogen, was required of both ECHA (2012) and SCOEL (2017) as noted in the Draft Assessment which stated (p. 417):

Expert review panels have determined that there is sufficient evidence to conclude that formaldehyde inhalation increases the risk for myeloid leukemia based on the results of epidemiological studies alone (NTP, 2011), or additionally supported by mechanistic research (NRC, 2014b; IARC, 2012a). Two European Union scientific bodies were not in agreement with those conclusions, noting that although there is evidence of associations between formaldehyde exposure and LHP cancers in the epidemiological literature, the observations are not biologically plausible since formaldehyde is not distributed to distal tissues preventing direct interactions in the bone marrow (SCOEL, 2017; ECHA, 2012). [Emphasis added.]

Although not cited in the Draft Assessment, the WHO, reached the same conclusion on formaldehyde and leukemia as did ECHA and SCOEL. Nielsen et al. (2017) in their re-evaluation of the WHO Indoor Air Quality Standard for Formaldehyde stated the following:

In the latest update of the NCI cohort (Beane Freeman et al. 2009), myeloid leukaemia risk was not increased at mean FA exposures below 1 ppm and peak exposures below 4 ppm and thus shows that preventing nasal cancer also prevents leukaemia. Remarkably, the previous follow-up study (Hauptmann et al. 2003) and the most recent follow-up (Beane Freeman et al. 2009) of the NCI cohort both showed an increase in Hodgkin's lymphoma at the average intensity ⩾0.5 ppm and peak exposures ⩾2 ppm. Hodgkin's lymphoma has not previously been associated with exposures to chemicals (Nielsen et al. 2013; Checkoway et al. 2015); known risk factors are, for example, socioeconomic status, family size and Epstein–Barr virus infection (c.f. Nielsen et al. 2013). Therefore, it is considered sufficient that the guideline is below these levels. On the whole, the nonlinear exposure–response relationships, the epidemiological effects at levels much higher than the WHO IAQG and the lack of consistency across studies indicate that the WHO IAQG is highly precautionary.

The NTP, IARC and NRC evaluations of formaldehyde were restricted to hazard identification. This is in stark contrast to the more recent WHO, SCOEL, or ECHA assessments of formaldehyde, which are risk assessment-based evaluations that must include an integration of evidence necessary to establish dose-

response assessments and a full hazard characterization. As such, the Draft IRIS Assessment should be benchmarked against competent authority evaluations performed under similar assessment guidelines. Additionally, any substantial deviations from other competent authorities conclusions must be documented and discussed in the Draft IRIS Assessment. Any further revisions to the Draft Assessment, must address the major differences between the derived no-effect levels (DNELs) and Occupational exposure limits (OELs) when compared to the RfCs and IURs proposed.

Example 4: The Draft Assessment often states the assessment followed EPA's Cancer Guidelines (U.S. EPA 2005), without citation. Likewise, there is no discussion of rationale for departing from the Guidelines when it did.

This is particularly obvious in descriptions of the MOA and its purported use to support dose response approaches. The Draft Assessment says the following (p. 2-79)

> *"...a large contribution from formaldehyde's mutagenic potential may be needed to explain formaldehyde carcinogenicity at low dose as well as in describing the observed tumor incidence. Finally, as discussed in Section 1.2.5, Evidence on mode of action for URT cancers, genotoxicity is itself thought to be one of the mechanisms by which formaldehyde exerts its cytotoxic action. Thus, it appears difficult to argue for a demarcation along the concentration axis of one MOA relative to the other. Therefore, because formaldehyde-induced tumors are not explained only by the cell proliferative MOA at any exposure, and since EPA does not develop an RfC specifically for one MOA when other MOAs also contribute to the tumor response, the use of an RfC approach is not preferred.*
>
> *Low-dose risk without extrapolating models below the observed data*
> *The various arguments presented in the last two paragraphs of the previous section on an RfC-like approach for cancer, particularly regarding formaldehyde's direct mutagenic potential, provide greater support for a low-dose linear approach in extrapolating low-dose formaldehyde cancer risk from the rat data. Following the procedures in EPA's cancer guidelines (U.S. EPA, 2005a) to be applied when knowledge of the MOA does not support an alternative approach or when direct mutagenicity does not contribute to the cancer response, this extrapolation was carried out as a straight line drawn to the origin from the HEC corresponding to the BMDL.*

The Cancer Guidelines recommend calculation of a Rfc when there is a demonstrated MOA supporting a threshold or non-linear approach. Furthermore, the Guidelines specify that more than one extrapolation method may be appropriate, rather than default to linear.

> *"When adequate data on mode of action provide sufficient evidence to support a nonlinear mode of action for the general population and/or any subpopulations of concern, a different approach — a reference dose/reference concentration that assumes that nonlinearity – is used. The POD is again generally an BMDL when incidence data are modeled. A sufficient basis to support this nonlinear procedure is likely to include data on responses that are key events integral to the carcinogenic process. This means that the POD may be based on these precursor response data, for example, hormone levels or mitogenic effects rather than tumor incidence data. When the mode of action information indicates that the dose-response function may be adequately described by both a linear and a nonlinear approach, then the results of both the*

linear and the nonlinear analyses are presented. ***An assessment may use both linear and nonlinear approaches if different responses are thought to result from different modes of action or a response appears to be very different at high and low doses due to influence of separate modes of action.*** *The results may be needed for assessment of combined risk from agents that have common modes of action."* [Bold added for emphasis]

And

Toxicokinetic models can improve dose-response assessment by revealing and describing nonlinear relationships between applied and internal dose.

And,

"...overt toxicity or qualitatively altered toxicokinetics due to excessively high doses may result in tumor effects that are secondary to the toxicity rather than directly attributable to the agent."

And,

"The qualitative question of whether an agent is absorbed by a particular route of exposure is important for weight of evidence classification, discussed in Section 2.5. Decisions about 2-27 whether route of exposure is a limiting factor on expression of any hazard, e.g., absorption does not occur by a specified route, are generally based on studies in which effects of the agent or its structural analogues have been observed by different routes, on physical-chemical properties, or on toxicokinetics studies."

And,

"...toxicokinetics studies may reveal effects of saturation of metabolic processes. These may not be considered key events in a mode of action, but they are given separate consideration in assessing dose metrics and potential nonlinearity of the dose-response relationship."

All of these factors were detailed in the Thompson et al. (2020) MOA for nasal tumors, and the Gentry et al. (2020) assessment of MOAs for leukemia. Neither of these publications were identified or discussed in the Draft Assessment. In contrast, all of these factors were dismissed for the mutagenic MOA for both NPC and leukemia. Then, in favor of using only selective epidemiology studies with non-statistically significant findings to establish a POD, the Draft Assessment deployed a low-dose linear modeling to develop IURs. This striking contrast must be addressed in any future draft of the IRIS formaldehyde assessment.

<u>Example 5: The Draft Assessment relies on multiple assumptions rather than considering alternative viewpoints supported by data in the formaldehyde literature</u>

Next, based on the conclusion in Section 1.2.5 that a mutagenic MOA was operative for Upper Respiratory Tract (URT) cancers, the unit risk estimate for NPC is adjusted for potential increased early-life susceptibility, in accordance with EPA guidance (U.S. EPA, 2005c) (see Section 2.2.4).

Section 1.2.5 gives a very different and contradictory story. First the Draft Assessment clearly states (p. 1-186) that:

Mechanistic data suggest that URT cancers are likely the result of genotoxicity and mutagenicity, cytotoxicity, and cell proliferation. Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when these factors are integrated, they form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis.

Then, on the very next page (p. 1-187), without any regard for what was just written, the Draft Assessment states:

The evidence is sufficient to conclude that a mutagenic mode of action of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

This conclusion is then carried forward to justify a linear low-dose extrapolation. This glaring discrepancy and very rough transition to a completely different position must be clarified and transparently communicated in any further drafts of the IRIS formaldehyde assessment.

Example 6: Discussion of MOA is more often speculative than grounded in empirical demonstration.

Mode of Action for Decrements in Pulmonary Function

This section of the document begins on page 1-62 with the statement that:

"Although an MOA for formaldehyde-related effects on pulmonary function remains incompletely defined, it is considered likely that these associations involve the indirect activation of sensory nerve endings in the lower respiratory tract (LRT) or increases in airway eosinophils, or both (see Figure 1-7)."

Then on the next page, language is more definitive that the MOA is not defined at all, when it is stated:

"As the mechanistic event(s) critical to understanding the observed relationship remain unknown, including how sensory endings in the LRT might be stimulated without distribution of inhaled formaldehyde to the LRT"

These statements are followed by a lengthy text that on possible MOAs leading to a conclusion, which is itself speculation rather than evidence:

"Overall, however, a definitive MOA has not been fully identified, several contributing mechanistic events interpreted with moderate to robust evidence appears to impact pulmonary function and, taken together, these data provide support for the biological plausibility of formaldehyde exposure-induced decreases in pulmonary function." [underlining added for emphasis]

Note also, that the studies listed in Table 1-10 on upper respiratory tract effects, use doses well above the zone of metabolic and removal process saturation and/or use unvalidated test methods.

It is recognized that at environmentally relevant concentrations (i.e., $\leqslant$2 ppm, the Occupational Safety and Health Administration (OSHA) short-term exposure limit (STEL)) formaldehyde is not distributed past the nasal passages/URT to the LRT. The conclusion from the Draft Assessment below is not supportable:

"The evidence indicates that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans." [Emphasis added].

This conclusion is made despite the fact that no one study evaluated reported long-term effects of formaldehyde inhalation on pulmonary function, using validated methods with exposures analytically quantified.

The Draft Assessment also concluded:

"The evidence is inadequate to interpret whether acute or intermediate-term (hours to weeks) of formaldehyde exposure might cause this effect." [underlining added for emphasis].

In addition, in other sections of the Draft Assessment, direct impacts of formaldehyde on the lower respiratory tract, even after long-term exposure, are dismissed, as stated (p. 1-143):

"Pathological findings in the LRT were generally not identified in higher confidence studies and are not discussed."

These contradictions and "plausible" speculations do not inform an evidence-based assessment. If there is no dose-response, not time concordance, and no mode of action for the observed effects, no pathological basis for the effects, and no distribution to the LRT, there is no support for any cause and effect relationship. The Draft Assessment would be improved by simply stating the evidence for and against causal association, without speculation about plausibility of undefined causes.

The Section "Evidence of Decrements in Learning and Memory" is highly speculative

On pages 1-355 to 1-359 of the Draft Assessment there is a discussion that purports to address mechanism.

"As appreciable amounts of formaldehyde are not expected to reach the systemic circulation or CNS to elicit direct effects, any potential mechanisms would need to be indirect. Thus, this section focuses on mechanisms that might secondarily result from alterations to the respiratory system (see Appendix A.5.6). As such, only data from formaldehyde inhalation studies are discussed, and confidence in the findings based on individual study evaluations is emphasized (see Appendices A.5.6 and A.5.7). Although none has been confirmed experimentally, several biologically plausible, but speculative sequences of mechanistic changes that might support indirect effects can be hypothesized based on the available formaldehyde-specific data, including . . . :" [underlining added for emphasis]

But p. 1-357 acknowledges that the text is purely speculative, perhaps hypothesis generating:

"In addition, it remains speculative to infer that changes in olfaction-related ascending pathways after formaldehyde exposure might modify neural cell populations that are likely to be unrelated." [underlining added for emphasis]

And the section ends on page 1-359:

"Overall, no MOA for potential formaldehyde-induced nervous system effects is available."

Such speculation is inappropriate, except perhaps in the context of generating hypotheses. Moreover, these discussions add unnecessary length to an already voluminous document. An evidence-based conclusion could have been framed in two paragraphs or fewer.

Evidence on the Mode of Acton for Developmental and Reproductive Effects

The Draft Assessment (pp. 409 – 411) provides a discussion that purports to describe "Evidence on Mode of Action for Developmental and Reproductive Effects" and potential mechanisms by which formaldehyde exposures might indirectly affect the reproductive outcomes following toxic insult at the portal of entry.

The section concludes with this.

> *"Nevertheless, no definitive data have been identified that define an MOA(s) explaining how developmental or reproductive outcomes might occur following inhalation exposure to formaldehyde."*
>
> Rather than providing evidence for MOA, the section speculates on possibilities:
>
> *"Plausibly, inflammatory mediators, ROS, or other factors observed in the blood could be operant in the reproductive or developmental outcomes by indirectly eliciting responses in the reproductive system or in the developing fetus" [underlining added for emphasis]*

An alternative to this speculation is provided below:

> "Effects reported were observed only at doses that overwhelm metabolic and other formaldehyde removal processes in the nasal cavity, resulting in maternal toxicity. As it has been demonstrated that formaldehyde does not distribute to systemic tissues, any observed toxicity to the reproductive system or in the developing fetus must be due to an indirect mechanism related to maternal toxicity. Thus, according to the Globally Harmonized System of Classification and Labeling and EPA guidance, formaldehyde is not classified as a reproductive or developmental toxicant."

The issues related to speculation regarding unsubstantiated hypotheses making the 2010 Draft Assessment unnecessary lengthy and speculation were previously raised by the NAS (2011) when they stated:

> *An additional hypothesis is that formaldehyde exposure at the port of entry induces secondary systemic effects, such as immune modulation or systemic inflammation, both of which are associated with LHP cancers. However, given the lack of direct data that could support those hypothetical modes of action, EPA could shorten those sections of the draft substantially and note that the modes of action remain uncertain.*

This needs to be addressed in any further drafts of the IRIS formaldehyde inhalation review.